VOLUME 1 • DECEMBER 1959 • NUMBER 6

A.M.A. ARCHIVES OF

NEUROLOGY

INDEX NUMBER

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Modification of Alpha-Wave Responsiveness to Light by Juxtaposition of Auditory Stimuli

Charles E. Wells

Inferior Nasal Quadrantanopsia in Pseudotumor Cerebri

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Archives of Neurology

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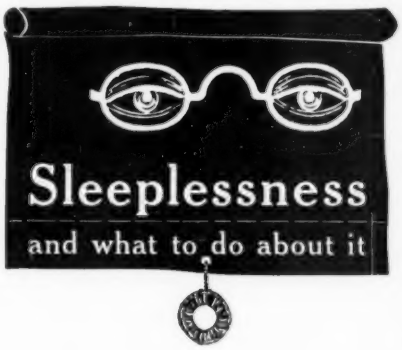

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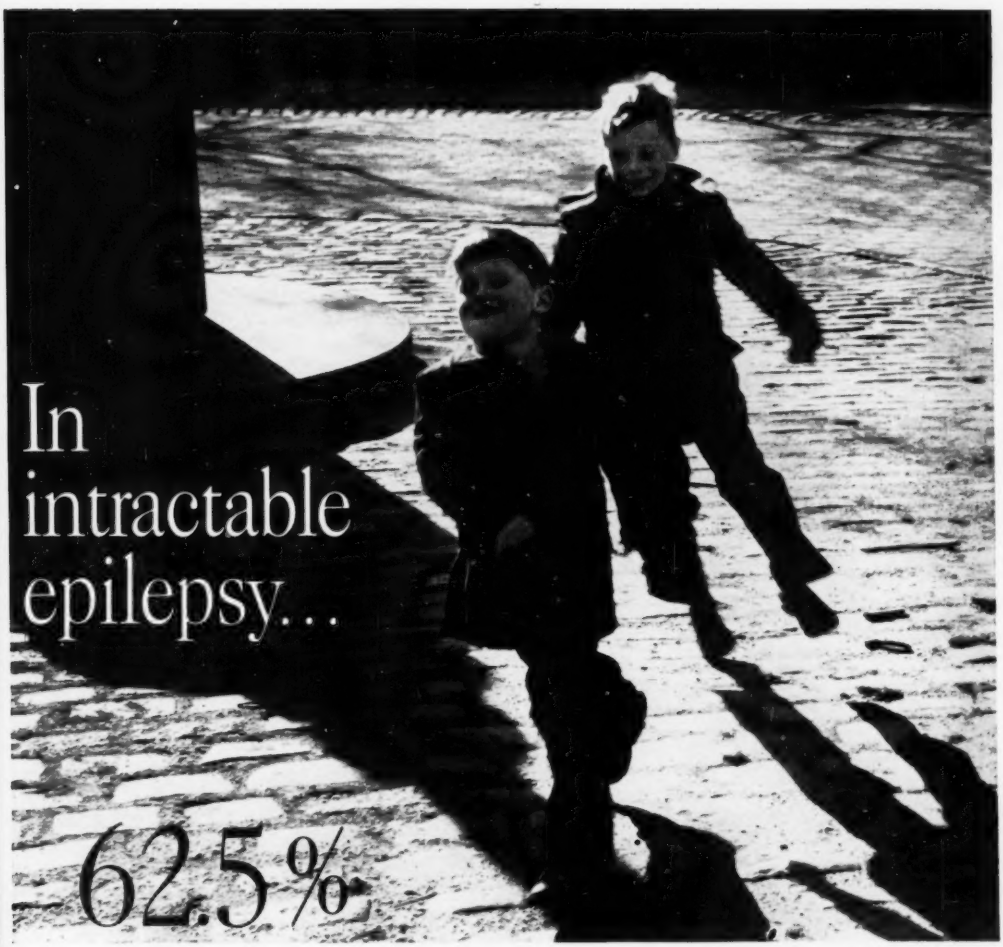

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Assistant Professor of Neurological Surgery
University of California School of Medicine
Los Angeles

and

CARL W. RAND, M.D.
Emeritus Professor of Neurological Surgery
University of Southern California School of Medicine
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Edited by
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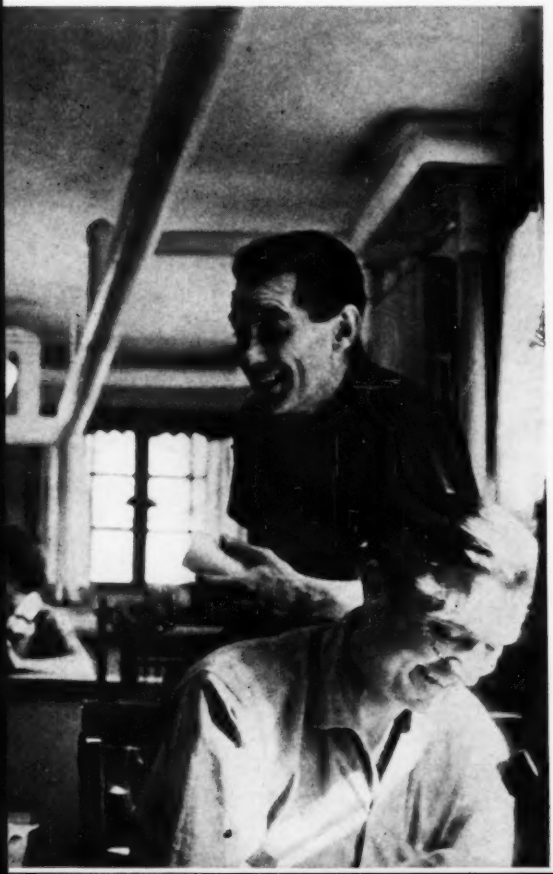

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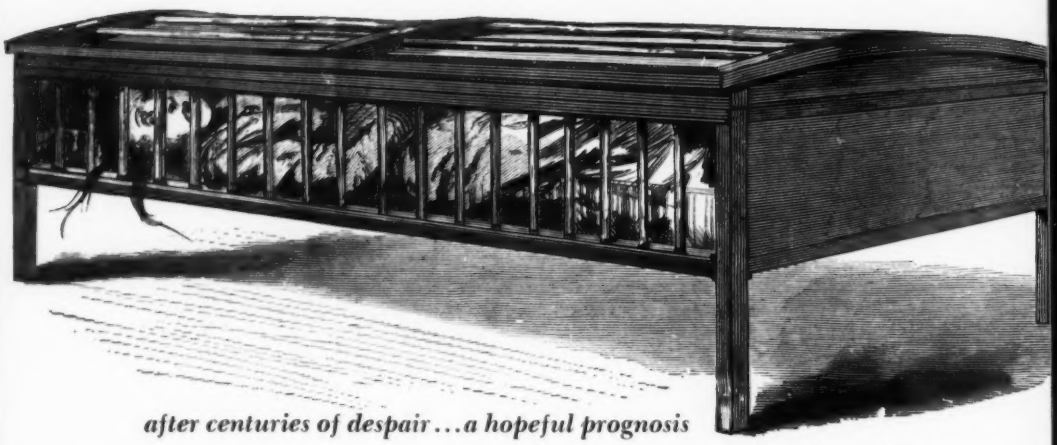

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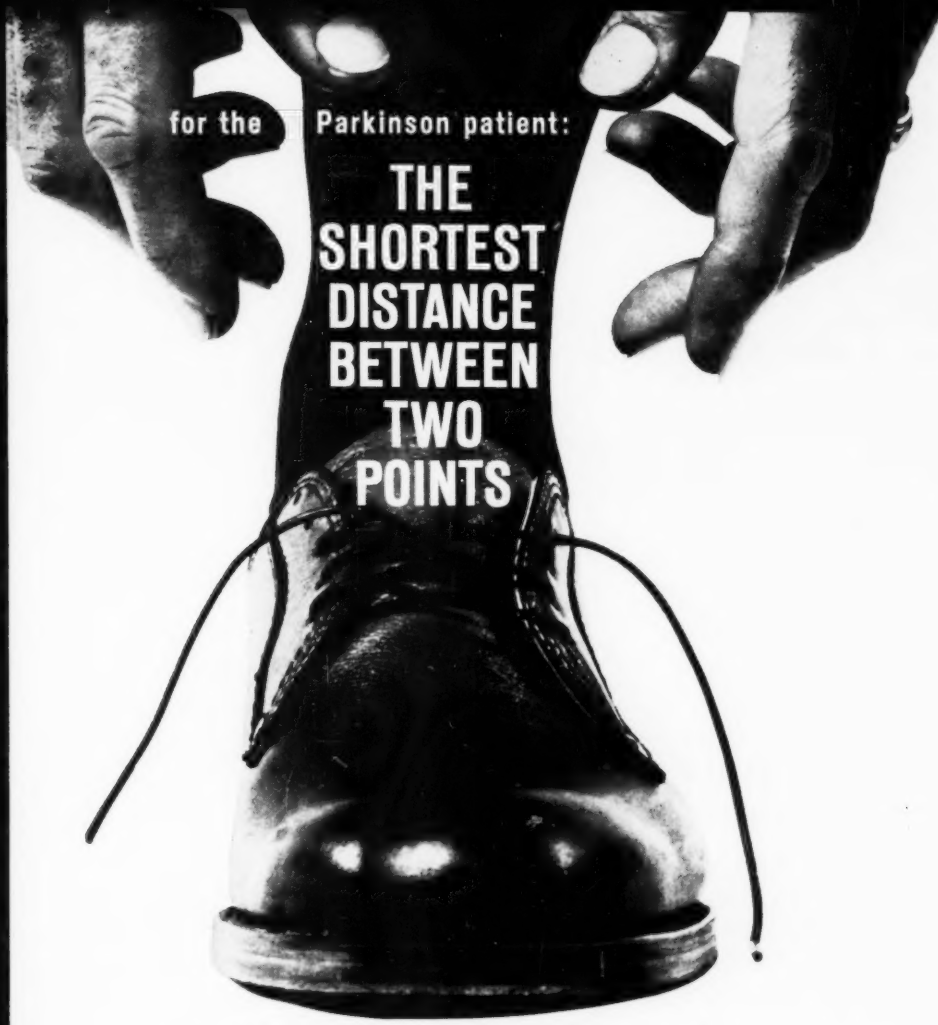

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A Restricted Form of Cerebellar Cortical Degeneration Occurring in Alcoholic Patients

MAURICE VICTOR, M.D.; RAYMOND D. ADAMS, M.D., and ELLIOTT L. MANCALL, M.D., Boston

Introduction
Clinical Observations
The Natural History of the Disease
Clinical and Pathological Case Reports
A Quantitative Estimation of the Changes in the Cerebellar Cortex
Comment
A. Clinical Features
B. Nature and Significance of the Pathological Findings
C. Clinical and Pathological Correlation
D. Etiological Considerations
E. Review of the Medical Literature
F. Spontaneously Occurring Cortical Cerebellar Degenerations in Animals
G. Restricted Cortical Cerebellar Degeneration in the Alcoholic Patient—a Clinical-Pathological Entity
Summary and Conclusions

Introduction

The relationship of cerebellar cortical degeneration to chronic alcoholism has been a controversial matter for many years. There are now several published accounts of a cerebellar syndrome in alcoholic patients, but these are purely clinical, and one has no way of ascertaining the nature of the pathological changes and of deciding whether they differed in any way from the other known types of cerebellar atrophy. Isolated, pathologically verified instances of primary cerebellar degeneration have been described in alcoholics, but, in general, the pathology has been incompletely described and the etiological relationship to alcohol has not been critically studied.

In the course of our own studies on the effect of alcohol on the nervous system, we have made clinical observations on a group of 50 patients, all of whom were undoubted and severe alcoholics and were afflicted with a remarkably uniform cerebellar syndrome. This syndrome was characterized, in almost every instance, by an ataxia of gait and of the legs, with relatively little involvement of the arms, speech, and ocular motility and, in the majority of cases, by an evolution over a short period of time, followed by years of stability. In seven of these patients a complete postmortem examination of the nervous system was made. Essentially, the lesion consisted of degeneration, varying in severity, of all neurocellular elements of the cerebellar cortex, particularly the Purkinje cells, with a striking topographical restriction to the anterior and superior aspects of the vermis and of the hemispheres. In addition to these seven patients, a similar cerebellar lesion was discovered in four others, in whom there had been a history of severe alcoholism but no indication of cerebellar

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TABLE 1.—*Summary of the Clinical Data on*

				Nutritional Status			Neurological			
Patient	Sex	Age of Onset, Yr.	Alcoholic History *	History of Inadequate Diet	General Signs of Malnutrition	Associated Deficiency Diseases	Gait	Legs	Arms	Speech
A	M	61	"Many" yr.; marital & economic difficulties	+	+	Wernicke-Korsakoff polyneuropathy 9 mo. before onset	+++	+++	+	+
B	M	44	21 yr.; 2 attacks of hallucinosis; arrests	+			+++	+++	+	0
C	M	42	25 yr.; numerous arrests				+++	+++	+	0
D	M	33	11-12 yr.; numerous arrests	+			+++	+++	+	+
E	M	53	"Many" years; peptic ulcer (?); G.I. bleeding	+	+	Polyneuropathy	++	+	+	0
F	M	55	31 yr.; derelict; numerous arrests	+	+	Polyneuropathy; ? pellagra	+++	+++	+	0
G	M	37	10-11 yr.; "rum fits"; delirium tremens; work difficulty	+	+		+++	+++	+	0
H	M	39	"Many" yr.; delirium tremens; attacks of hallucinosis	+	+	Polyneuropathy	+++	+++	+	0
I	M	52	25 yr.; arrests				+++	+++	+	+
J	F	37	17 yr.; "rum fits"; delirium tremens	+	+	Polyneuropathy; Wernicke-Korsakoff 3 mo. after onset	+++	+++	0	0
K	M	38	15-20 yr.	+		Polyneuropathy	+++	+++	+	0
L	M	47	26 yr.; marital & economic difficulties; numerous arrests	+	+		+++	+++	+	0
M	M	58	21 yr.; steady spree; arrests; halluc.; loss of jobs; divorce	+			++	+	+	0
N	M	45	9 yr.			Polyneuropathy	+++	+++	0	0
O	M	39	12 yr.; delirium tremens; numerous arrests; divorced; peptic ulcer				+++	+++	+	0
P	M	49	"Many" yr.; peptic ulcer; arrests; father alcoholic	+	+	Polyneuropathy	++	++	+	0
Q	M	63	"Many" yr.; "rum fits"; peptic ulcer	+	+	Polyneuropathy	++	++	+	0
R	M	53	23 yr.; delirium tremens; father alcoholic	+	+	Polyneuropathy; retrobulbar neuropathy	+++	+++	+	0
S	M	55	More than 25 yr.; work difficulties	+	+	Polyneuropathy	+++	+++	+	0
T	M	39	"Many" yr.	+	+		+++	+++	++	++
U	M	60	More than 25 yr.; loss of job; D.T.'s	+	+	Polyneuropathy	++	+++	+	0
V	M	54	22 yr.; delirium tremens; divorced; arrests; father alcoholic				+++	+++	+	0
W	F	55	"Many" yr.	+	+	Polyneuropathy	++	++	0	0
Group IIa										
X	M	37	20 yr.; delirium tremens; divorced				+++	+++	+	0

Fifty Alcoholic Patients with Cerebellar Disease

Examination				Course			
Nystagmus	Instability of Trunk	Others	General Physical Abnormalities	Progression	Stability	Total Duration of Illness	Comment
+	+		Pulmonary tbc; hepatomegaly	Weeks to months	6 yr.	6½ yr.	Abstinent at time of onset of cerebellar disease
0	+	Hypotonia		"Overnight"	9 yr.	9 yr.	Unusually abrupt onset
+	+	Hyoptonia	Seborrheic dermatitis	6 wk.	15 yr.	15 yr.	
+	+	Ocular dysmetria		Several mo.	21 yr.	21½ yr.	Case 2., Romano, Michael, & Merritt[***] (1940)
0	+		Cirrhosis	1-2 mo.	1 yr.	1 yr.	Died of Ca larynx, (pathological Case 6)
+	0			Abrupt onset while crossing street	3 yr.	3 yr.	Unusually abrupt evolution
+	+			2 mo.	5 yr.	5 yr.	
0	0		Acne rosacea; cirrhosis	Several mo.	3 yr.	3½ yr.	
+	+	Ocular dysmetria	Mild hypertension	Several wk.	2 yr.	2 yr.	
0	+			3-4 mo.	3 yr.	3¼ yr.	Abstinent for several weeks before onset; trauma (?)
++	+			4 mo.	8 yr.	8¼ yr.	
+	+		Cirrhosis; acne rosacea	12 mo.	4 yr.	5 yr.	
0	+	Head tremor; hypotonia		Few weeks	1 yr.	1 yr.	Trauma (?)
0	+	Hyoptonia; tremor of head		Less than 1 yr.	12 yr.	13 yr.	
0	+	Hypotonia; postural tremor		Several mo.	12 yr.	12½ yr.	Influenza, 1918
0	0			Several wk. or mo.	3 yr.	3¼ yr.	
+	+		Cirrhosis	Several wk. to mo.	3 yr.	3¼ yr.	
0			Cirrhosis	Several wk.	1 yr.	1 yr.	Died hepatic coma; (pathological Case 3)
0	+	Tremor head; postural tremor		3-4 wk.	2 mo.	¼ yr.	
++	+	Hyoptonia		1-3 mo.	12½ yr.	12¾ yr.	
0	0	Hyoptonia	Hepatomegaly	Abrupt	6 mo.	½ yr.	Abstinent at time of onset of cerebellar disease
0	+		Hypertension	4-6 mo.	3 yr.	3½ yr.	
0	+		Cirrhosis	2 mo.	1 yr.	1 yr.	
+	+		Hepatomegaly	2 yr.	3 yr.	5 yr.	

TABLE 1.—Continued

Y	M	45	30 yr.; arrests; severe family history; peptic ulcer	+	+	Polyneuropathy	+++	+++	+	0
Z	M	44	23 yr.; social difficulties	+	+	Polyneuropathy; retrobulbar neuropathy	+++	+++	+	+
Aa	M	48	25 yr.; work difficulties; arrests	+		Polyneuropathy	+++	+++	+	+
Ab	M	47	27 yr.			Polyneuropathy	+++	+++	+	0
Ac	M	46	26 yr.; arrests; father and 2 brothers alcoholic				+++	+++	+	0
Ad	M	43	13 yr.; father and brother alcoholic	+		Polyneuropathy	+++	+++	0	0
Ae	M	44	20 yr.; father and 1 brother alcoholic	+	+	Polyneuropathy	+++	+++	+	0
Af	M	31	15 yr.; delirium tremens		+		+++	+++	+	+
Group IIb										
Ag	M	43	"Many" yr.; delirium tremens	+	+		+++	+	+++	++
Ah	M	62	"Many" yr.; delirium tremens	+	+	Polyneuropathy	+++	+++	+	+
Ai	M	49	14 yr.; divorce; numerous arrests	+			+++	+++	++	+
Aj	M	49	20 yr.; arrests; difficulty with work				+++	+++	+	+
Ak	F	39	25 yr.; hallucinosis; delirium tremens	+	+	Polyneuropathy	+++	+++	+	0
Al	M	32	7 yr.				+++	+++	+	+
Am	M	55	"Many" yr ; father, 1 brother alcoholics				+++	+++	+++	++
Group IIIa										
An	M	32	"Many" yr.; numerous attacks; delirium tremens	+	+	Wernicke's disease and polyneuropathy 2 yr. before worsening of cerebellar signs	+++	+++	+	+
Ao	M	36	16 yr.; arrests; economic difficulties	+			++++	++++	+++	+++
Ap	F	46	20 yr.	+	+		+++	+++	+	0
Aq	M	42	10 yr.; work difficulties	+	+	? Polyneuropathy	+++	+++	++	0
Ar	M	?27	Since age 16	+			+++	+++	++	+
Group IIIb										
As	M	42	20 yr.; never worked			Polyneuropathy	+++	++	+	0
At	M	Not known	41 yr.; delirium tremens and hallucinosis, several attacks	+			++	+	+	0

TABLE 1.—Continued

0	+	Hypotonia		18 mo.	7 yr.	8½ yr.	
+	+	Ocular dysmetria		4 yr.	4 yr.	8 yr.	
0	+	Ocular dysmetria; hypotonia	Mild cirrhosis	2 yr.	1 yr.	3 yr.	
+	+	Tremor head		15 yr.	4 yr.	19 yr.	Syphilis age 23; adequately treated
+	+	Congenital abducens palsy	Hepatomegaly	13 yr.	2	15 yr.	
0	0		Cirrhosis	2 yr.	10 yr.	12 yr.	Blood serology pos.; died of intraperitoneal hemorrhage; (pathological Case 1)
+	+	Tremor head; hypotonia	Acne rosacea; cirrhosis	7 yr.	6 yr.	13 yr.	
0	0		Hepatomegaly	6 yr.	6 yr.	12 yr.	
0	+	Tremor of head; postural tremor		13 yr.	0		Unusual distribution of cerebellar signs
0	+		Hypertension	7 yr.	0	7 yr.	
0	+	Tremor head; postural tremor		6 yr.	0	6 yr.	5 wk. abstinence prior to onset
0	+	Postural tremor		7 yr.	0	7 yr.	
0	+		Cirrhosis	6 yr.	0	6 yr.	Died of hepatic coma; (pathological Case 2)
+	+	Hypotonia		12 yr.	0	12 yr.	
	+			10 yr.	0	10 yr.	Familial tremor; healed tbc (pathological Case 5)
++	+	Titubation of head		Mild gait disturbance 12 yr.; rapid worsening 6-8 wk. at age 44	4 yr.	16 yr.	Rapid worsening associated with severe febrile illness (pneumonia)
+	+++	Tremor of head; postural tremor; hypotonia	Hepatomegaly	Mild gait disorder 14 yr.; rapid worsening several mo.	2 yr.	16 yr.	Influenza, 1918
0	+			Mild disorder of gait 4-5 yr.; rapid worsening 7-8 mo.	3 yr.	8 yr.	
0	0	Hypotonia		Mild disorder of gait, 18 mo.; rapid worsening days to wk.	1½ yr.	2 yr.	
0	+	Tremor of head; hypotonia	Hypertensive; hepatomegaly	Mild disturbance of gait and speech since early adult life; worsening over 5 yr. period, age 58-63	3 yr.	?40 yr.	
++	+	Titubation of head		No known progression	20 yr.	20 yr.	
0	0		Advanced cirrhosis	Unknown	"Many" yr.	"Many" yr.	Died of ruptured esophageal varices; no autopsy

TABLE 1.—Continued

Group IV										
Au	M	56	"Many" yr.; peptic ulcer; loss of jobs		+	Korsakoff's psychosis	+++			
Av	M	56	30 yr.; delirium tremens; work and marital difficulties	+	+	Polyneuropathy, mild Korsakoff's psychosis	+++	+++	0	+
Aw	M	60	At least 25 yr.; peptic ulcer; pancreatitis; father alcoholic	+	+	Polyneuropathy	++		0	+
Ax	M	Unknown	30 yr.	+	+	Polyneuropathy	+++	++	+	0

* Number of years indicates the duration of excessive drinking prior to the onset of cerebellar symptoms.

disease during life. The study of this material has convinced us that there does exist a clinical-pathological entity which bears a relationship to the excessive imbibition of alcohol, or, perhaps more likely, to an associated nutritional defect. It is in support of this proposition that we are presenting a detailed account of our findings.

In the course of this study the medical literature dealing with cerebellar degeneration was extensively reviewed. This has enabled us to differentiate the cerebellar degeneration associated with alcoholism from cerebellar cortical degeneration of other types. Also, on the basis of this review, we have attempted to classify anew the cerebellar cortical degenerations of all types.

Clinical Observations

Clinical observations have been made on a group of 50 patients, of whom 46 were men and 4 were women. Twelve patients were seen at the Boston City Hospital, where the study was begun. These patients were representative of the lower economic and social classes of the city, and were all studied prior to July, 1951. Since that time, 34 cases have been seen on the neurological ward and in the clinics of the Massachusetts General Hospital, 3 at the Veterans Administration Hospital, Togus, Maine, and 1 at the Veterans Administration Hospital, West Roxbury, Mass. This group of 38 patients was drawn from a more extensive geographical area, i.e., all of New England, and from a less restricted economic class than the original one. The clinical features of this group of patients are summarized in Table 1.

Of the entire 50 patients, all but 4 were personally examined and followed for varying periods of time. These latter four (Table 1, Au, Am, Aa, R) were the patients in whom the presence of cerebellar degeneration first came to our attention at postmortem examination; careful questioning of friends and relatives and a review of the clinical records disclosed that cerebellar symptoms had been present during life, and these were described clearly enough to justify the inclusion of these patients in the study.

Despite the well-known difficulty in eliciting a precise history of alcoholic drinking habits, we had no doubt that every patient included in this study had been an inveterate and grossly excessive drinker of many years' duration. Two patients stated that they had been drinking heavily for seven and nine years, respectively, before the onset of neurological symptoms. All the others admitted to an excessive intake for periods longer than 10 years before the onset of symptoms. Indeed, in 16 instances the duration of drinking was over 25 years. No particular type of alcoholic beverage could be incriminated. Although whisky was the preferred drink, most of the patients consumed ale and wine as well, the choice of beverage ultimately depending on what the patient could afford. Forty patients could be designated as steady drinkers, meaning that there was a constant daily overindulgence. Eight patients stated that they drank periodically for several consecu-

TABLE 1.—Continued

			Unknown	Unknown	Less than 2 yr.	Died of intestinal obstruction; (pathological Case 7)
0	0		At least 6 mo.	Unknown		Syphilis, age 21, treated; no follow-up after initial exam
+		Advanced cirrhosis	Unknown	Unknown	3 mo.	Died in hepatic coma (pathological Case 4)
0	+	Advanced cirrhosis	Unknown	Unknown	Unknown	No follow-up after initial exam.

tive days or weeks, with varying periods of abstinence between discrete drinking bouts. For the remaining two patients a detailed description of their drinking habits was not available. Most of the patients had experienced one or more serious complications of alcoholic excess prior to the onset of their cerebellar disease. About half of them had suffered a serious dislocation in their social, economic, or marital life. Delirium tremens had occurred in 14 patients, hallucinosis in 4 patients, and "rum fits" in 3 others.

There was evidence from the history and examination that a serious disturbance of nutrition had occurred in the majority of patients. Dietary history disclosed that in 36 patients the food intake had been grossly inadequate for many months, or even years, before the onset of cerebellar symptoms. Furthermore, in three patients who gave a history of adequate diet, examination disclosed signs of poor nutrition in terms of a mild polyneuropathy. Twenty-nine patients had physical stigmata of undernutrition when they first presented themselves with their cerebellar disorder. These took the form of loss of muscle bulk and subcutaneous tissue, redness and depapillation of the tongue, dryness and thinness of skin, and so forth. Twenty-three patients had signs of polyneuropathy. These signs were always limited to the lower extremities and were never severe in degree, consisting of a loss or depression of the tendon reflexes, muscle weakness, and blunting of superficial and vibratory sensation in the feet and lower legs; position sense was generally well preserved. In five patients there was evidence of a previous attack of Wernicke's encephalopathy, and in yet another two there was a clearly documented history of retrobulbar neuropathy. Disease of the liver was present in 23 patients; in 14 this was severe enough to be classified as Laennec's cirrhosis; in 9 others hepatomegaly had been observed but was not further investigated. On the other hand, 11 patients showed no signs of nutritional abnormality when they were first seen by us, nor did they give a history of inadequate diet. This does not necessarily mean that malnutrition was not a factor in these patients. Two of them (Table 1, Au, Am) came to our attention only after death, and their dietary habits could not be ascertained. The other nine sought medical help only long after the onset of their illness (6 months to 13 years), at which time their alcoholic, and perhaps their dietary, habits had changed considerably.

Aside from alcoholism and nutritional depletion, the past medical history disclosed little of importance. Three patients (Table 1, Ad, Ab, Av) had a history of previous syphilitic infection, many years before the onset of their cerebellar symptoms; two of these must have been adequately treated, since neither had a positive blood or spinal fluid serology when first seen by us. The third patient (Ad) had a positive blood serology but no other clinical or spinal fluid evidence of syphilis. In one patient there was a past history of pulmonary tuberculosis, and in another tuberculosis was first discovered a year after the onset of cerebellar symptoms. Three pa-

tients had suffered an attack of influenza during the 1919 pandemic.

A detailed family history was elicited from 16 patients. Alcoholism had been a major problem with the fathers and brothers of 10 patients. In none of the relatives was there a disease which could possibly have been cerebellar in nature, although there was one instance of "familial tremor."

The age of onset of the cerebellar symptoms could be determined in 47 cases. The earliest age of onset was 31 years; the latest, 63; the average, 46.3. In 11 patients the illness developed in the fourth decade of life; in 19, in the fifth; in 12, in the sixth, and in 5, in the seventh. Fully two-thirds of the patients acquired their disease before the age of 50.

With only two exceptions, the initial complaint in all the patients was referable to an abnormality of gait, and was variously described as "weak legs," "rubber legs," "slowing up," staggering, stumbling, unsteadiness, or loss of balance. These remained the major complaints throughout the illness, although later other symptoms were added, such as incoordination and tremor of the arms (seven cases), thickness of speech (six cases), cramps, shooting pains, "numbness," and burning or tingling in the legs (five cases, in three of which polyneuropathy existed), and intermittent diplopia or blurring of vision (three cases). In one patient abnormalities of gait, arm movements, and speech were noted simultaneously; in another, a disturbance of handwriting was the original symptom, with subsequent affection of speech and gait.

Examination disclosed a constellation of signs which was remarkably uniform from patient to patient. A summary of these signs is recorded in Table 2. As one might expect from the symptomatology, the most prominent abnormalities were those of stance and gait. A disorder of these functions was present in every case, and was considered of severe degree in 42 patients. Characteristically the patient stood with his feet placed far apart, his trunk pitched forward slightly, and arms held stiffly and somewhat away from his sides. In most of the patients there was an instability of the trunk of varying severity, and in 11 patients there was an independent rhythmic tremor of the head on the trunk. These postural abnormalities were accentuated during ambulation. The patient progressed slowly and haltingly, with small, irregular steps, his eyes fixed on the ground before him, and he lurched unpredictably in all directions. The ataxia was greatly accentuated under circumstances which required rapid postural adjustments, such as the initiation of walking, turning, avoiding obstacles, or coming to a halt and sitting down. All of these features were regarded as distinctly cerebellar in nature.

As the disease stabilized, the gait became somewhat altered. The terms "reeling" or "drunken," so often used to designate the abnormality of gait in acute cerebellar disease or in alcoholic intoxication, no longer seemed appropriate. The alteration of gait in the chronic, stable stage of the disease

TABLE 2.—*Summary of the Cerebellar Signs in Fifty Patients*

	Severe	Moderate	Mild	Absent	No Information
Ataxia of gait	42	8	0	0	
Incoordination of legs	38	6	4	0	2
Incoordination of arms	4	3	36	6	1
Nystagmus	0	4	16	28	2
Dysarthria	2	2	14	31	1
Truncal instability	1	1	36	9	3
Tremor of head	1	0	10	34	5
Hypotonia			14		
Ocular dysmetria			4	44	2
Postural tremor	1	0	5	39	5

was in itself distinctive. The patient still walked slowly; but his steps, though smaller than normal, were now more regular than before. The gait assumed a lilting, rhythmical quality, for which the term "rubber legs" was particularly appropriate. In this way the patients were able to walk for long distances, if unimpeded. Although this gait still appeared unnatural, it no longer, in itself, conveyed the full degree of disability. The patient's instability became much more apparent when he was required to make rapid postural adjustments and when he was subjected to special neurological tests, such as tandem walking. In fact, heel-to-toe walking was virtually impossible for these patients, even for those with the mildest form of the disease.

In only one patient (Ao) was the gait so severely affected as to confine him to bed. All the others were capable of getting about, although many of them required some support, usually a cane. Many of the patients made the interesting observation that just the slightest contact with some object close at hand, such as a hedge or the side of a desk, had a remarkably steadying effect. We were able to verify this observation on numerous occasions.

Apart from the movements entailed in walking, individual movements of the legs were severely affected in 38 of the patients, and to a less degree in 9 others. This affection took the form of a characteristic cerebellar incoordination, best demonstrated on heel-to-shin testing. In contrast to the legs, the arms were but little affected; in 6 cases, in fact, no abnormality could be detected, and, of the remainder, 37 showed only slight slowness and clumsiness of rapidly alternating movements and perhaps a terminal wavering on finger-to-nose testing. In the latter group the handwriting was often badly affected, seemingly out of proportion to the other motor defects in the arms (Fig. 1). A moderate or severe degree of cerebellar incoordination and intention tremor in the upper extremities was present in only seven instances.

Speech function was even less consistently affected. In 31 cases it was judged to be normal. In 18 patients there was an abnormality of speech which was slight in degree and which took the form mainly of slowing and slurring; in only 3 of these could the abnormality be designated as scanning in type.

Similarly, nystagmus was entirely absent in 28 patients and was a prominent finding in only 4 of the remainder. In all affected patients the nystagmus was horizontal and demonstrable only on lateral gaze, although in two patients it also had a rotary component. In addition, four patients exhibited an ocular dysmetria, i.e., pendular excursions of the eyes (overshooting) before attaining fixation (Cogan [1]).

A statement regarding the exact incidence of hypotonia cannot be made from our observations. Pendular knee jerks or "rebound" phenomena, if these be taken as signs of hypotonia, were found in 14 patients. Only one patient had hyperextensibility of the knee joints. Apart from these signs, we did not feel confident in judging accurately the presence or absence of hypotonia. None of the patients exhibited spasticity or rigidity of the musculature, at least of the type which one associates with disturbances of the corticospinal tracts or of the basal ganglia. However, in many of them there was a tightness and tenseness

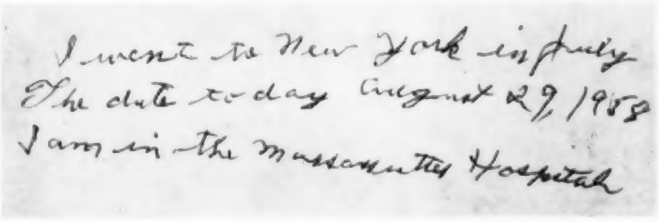

I went to New York in July
The date today August 29, 1958
I am in the Massachusetts Hospital

Fig. 1.—Impairment of handwriting in a patient who otherwise showed minimal cerebellar signs in the arms.

of the trunk and leg muscles, an abnormality which was not detectable when the patients were supine but appeared when they stood or walked without support. This abnormality disappeared completely, or nearly so, when the patients had some means of support, such as a cane or a railing.

Six patients showed an unusual tremor, which in no way resembled the characteristic intention tremor of cerebellar disease. This was a rhythmical tremor and appeared only with certain sustained postures. At times it took the form of an adduction-abduction or flexion-extension movement of a finger or two, as, for example, when the patient wrote or supported his weight partially on his hands. At other times the proximal musculature of the limbs was involved, and a tremor of the thigh appeared when the patient was seated, or of the arms when they were outstretched. Although in tempo this tremor was like that of Parkinsonism, i.e., 3 to 5 per second, the affection of the proximal musculature of the limbs in severe instances was more reminiscent of the tremor of hepatolenticular degeneration (Wilson's disease).

Cerebellar catalepsy (sometimes referred to as the Babinski phenomenon) was notably absent in our patients. This phenomenon is supposedly characterized by the ability of the patient to maintain an immobile posture of the lower extremities for an unusually long period while he is in the supine position with his legs flexed at the hips and knees. In fact, this maneuver tended to bring out a coarse, irregular instability of the legs, particularly of the thighs, which was so violent at times that the entire trunk rocked on the bed.

Ancillary examinations disclosed no consistent abnormalities. The blood counts, urinalyses, and blood chemistry determinations were abnormal only in the patients with associated medical illnesses, particularly those with liver disease and intercurrent infections. In no case was there an eosinophilia. The spinal fluid was examined in 32 patients; in 4 of these a slight elevation of protein (50-60 mg. %) was present. However, the colloidal gold curve was normal in all, and there were no other abnormalities. Pneumoencephalograms were obtained on only three patients, but they were abnormal in each case, showing a dilated fourth ventricle and cisterna magna and a shrunken cerebellum with abnormally wide sulci. These findings are in keeping with those described by Murphy and Arana [2] and by Uzman.[3]

None of our patients complained of tinnitus, vertigo, or deafness. Four of them (Ae, H, O, M) were subjected to hearing and vestibular function (caloric) tests, and no significant abnormality was found. A number of other negative features should be briefly mentioned. Intellectual deterioration was not a feature in our patients, with the exception of three who had suffered an attack of Wernicke's disease and Korsakoff's psychosis, and who showed the characteristic cognitive abnormalities of that syndrome. Myoclonus epilepsy was not present in any of the patients under discussion, and skew deviation of the eyes was never found.

The Natural History of the Illness

Perhaps the most interesting clinical feature to emerge from this study concerned the natural history of the illness, i.e., its mode of evolution and progression. An opportunity to study this facet of the illness was afforded by the fact that most of the patients were personally observed over a period of many years. Of the 50 patients, only 4 could not be assessed from this point of view, since an adequate account of the evolution and progression of their illness was not obtained. The remaining 46 patients could be divided into three categories (Table 1 and Fig. 2).

The first, and largest, group consisted of 23 patients. In these the disease evolved rapidly, the maximum deficit being attained after a period of several weeks or months. In two patients of this group the evolution

TABLE 3.—*Summary of the Neuropathological Changes in Eleven Alcoholic Patients with Cerebellar Cortical Degeneration* *

Case	1	2	3	4	5	6	7	8	9	10	11
Cerebellar Cortex											
Lingula	+	+	+	+	+	+	+	+	+	+	+
Central lobule	+	+	+	+	+	+	+	+	+	+	+
Culmen	+	+	+	+	+	+	+	+	+	+	
Declive	+	+	+	+	+	+		+	+		
Folium	+	+									
Tuber	+										
Pyramis	+	+			+						
Uvula	+	+									
Nodulus	+	+				+					
Anterior lobes	+	+	+	+	+				+		
Simple lobules	+	+									
Ansiform lobules		+									
Flocculus	+	+									
Dorsal parafloccullus	+	+									
Deep cerebellar nuclei											
Dentate	+	+	+			+			+		
Intermediate (globose and emboliform)	+	+	+		+				+		
Fastigial	+	+	+	+	?	+			+		
Olivary complex											
Dorsal acc. olive	+	+	+		+	+		+		+	
Medial acc. olive	+	+			±	+		+			
Inferior (principal olive)	+	+	+	±	+	+		+	+	+	
Vestibular complex											
Superior	+		+		+	+	?		?	?	?
Lateral	+						?		?	?	?
Medial	+										
Spinal	+	+									
Associated disease											
Wernicke's disease	+					+	+	+			
Polyneuropathy	+	+	+	+	+						
Hepatic encephalopathy	+	+	+	+					+	±	
Optic neuritis			+								

* The plus sign (+) indicates the presence of alteration without regard to degree of change; question mark (?) indicates that the structure concerned was not available for study.

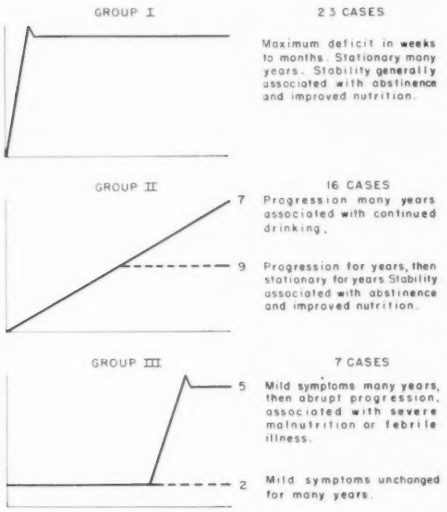

GROUP I
23 CASES
Maximum deficit in weeks to months. Stationary many years. Stability generally associated with abstinence and improved nutrition.
GROUP II
16 CASES
7
Progression many years associated with continued drinking.
9
Progression for years, then stationary for years. Stability associated with abstinence and improved nutrition.
GROUP III
7 CASES
5
Mild symptoms many years, then abrupt progression, associated with severe malnutrition or febrile illness.
2
Mild symptoms unchanged for many years.

Fig. 2.—Diagrammatic representation of the natural history of the illness in 46 cases.

of the illness was apparently even more abrupt. One of them (F) first noticed unsteadiness when he was forced to hurry across a street to avoid an oncoming automobile; he insisted that the disturbance of gait had not worsened since that incident. The other (B) first became aware of unsteadiness on arising one morning, although none had been present the night before; he also claimed that there had been no worsening thereafter. The veracity of these statements may well be doubted, but, in any event, once the maximum intensity of the illness had been attained, the cerebellar symptoms remained essentially unchanged for many years, in one case as long as 21 years after the onset. Our own observations, extending over a period of years, affirmed the stationary character of the cerebellar ataxia.

The second group comprised 16 patients, and in them the disease evolved in a slow, gradual fashion over a period of several years. In seven patients of this group the symptoms and signs were alleged to have worsened steadily throughout the period of observation (6 to 13 years). In the remaining nine patients, there was also a long period of steady progression (from 18 months to 15 years), but the clinical condition eventually stabilized and then remained unchanged for periods of 1 to 10 years.

In the third group, consisting of seven patients, mild stationary signs of cerebellar disease had been present for several years. On this background there occurred in five of them a relatively rapid worsening of their cerebellar signs, to be followed, in turn, by a period of stabilization. In four of these five patients the worsening occurred over a short period of time and could be measured in weeks or months; in the fifth (Ar) the worsening was somewhat slower.

It is appropriate at this point to examine the clinical factors which may have been associated with the onset of abrupt worsening of the cerebellar syndrome, particularly the role of alcoholism and/or malnutrition. Although all the patients had been drinking excessively for many years, there was no indication that the intake of alcohol had been significantly increased in the period just before the onset of the illness. In fact, six patients had actually been abstinent for varying periods of time just prior to the onset of their cerebellar symptoms. Two patients (J, M) were admitted to the hospital after trauma, where, in the convalescent period, they first developed a characteristic cerebellar syndrome. A third patient (U) was hospitalized in a tremulous state, following the cessation of drinking. Several days later he developed full-blown delirium tremens; and on recovery from this state, a week later, he first noted a disturbance of gait. Another patient (Ai) first developed cerebellar symptoms after a five- or six-week period of abstinence following surgery for varicose veins. A fifth patient (An), who had had a mild gait disturbance for many years, became severely ataxic while in the hospital recovering from an attack of lobar pneumonia. Yet another patient (A) had been committed to the state hospital with Korsakoff's psychosis. Eight months later, during which period he had no access to liquor, he was found to have a gross cerebellar ataxia. It is noteworthy that he was a distinct feeding problem throughout this eight-month period, and that advanced pulmonary tuberculosis was recognized shortly afterward.

It has already been mentioned that in 38 patients there was a history of poor nutrition for many months or years preceding the cerebellar disease. In nine instances, a particularly severe degree of weight loss had occurred within a short period before the onset or the sudden worsening of cerebellar symptoms (Cases Ao, I, L, Ar, S, Ae, K, M, Aq).

In general, the progression of the cerebellar symptoms and signs was associated with continued drinking and poor nutrition. In one patient (Al), however, the cerebellar disease was reportedly slowly progressive for seven years, despite a reduction in alcoholic consumption and despite adequate dietary intake. Conversely, stabilization of the disease process was usually associated with the cessation or marked reduction of drinking and with improvement in nutrition. Of 37 patients in whom stabilization followed a period of progression, only 6 had not altered their drinking habits. Thirty-one patients had indeed become totally or relatively abstinent after the onset of their illness. This was probably not the result of medical advice but followed the discovery that the ingestion of even small amounts of alcohol would markedly increase their disability.

Once the cerebellar signs became fully established, they always remained to a greater or less extent. In some patients there was a distinct, though only partial, improvement in gait over a number of years.

It was felt that this improvement was not attributable to any single factor, but probably resulted from a combination of factors, such as improvement in general health and nutrition, recovery from the effects of a mild polyneuropathy, and gait retraining.

Clinical and Pathological Case Reports

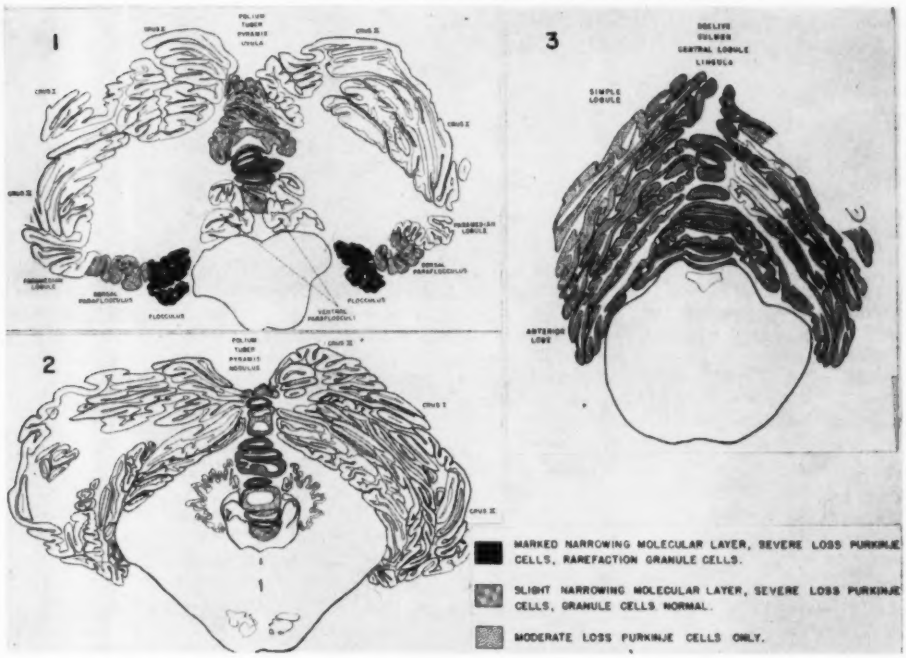
Our pathological data have been derived from the study of the nervous systems of 11 patients. Seven of these clearly had evidence of cerebellar disease during life, and they were among the patients whose clinical features have been summarized in Tables 1 and 2. In the case reports which follow, each of these patients is designated by a letter, or letters, which serve to identify him in Table 1.

Four cases of cerebellar disease were discovered in the course of examining the nervous system of patients afflicted with other complications of serious alcoholism. They have been included in this portion of the study, since the pathological changes were identical with those of the first seven cases. There was no evidence, however, that a cerebellar syndrome had existed during life.

A detailed clinical and pathological description of these 11 cases follows, and a summary of the pathological findings is appended. The topography and severity of the lesions are illustrated by a number of diagrams, drawn to scale from actual horizontal or sagittal sections of the cerebellum taken from each case (Figs. 3 to 9). In addition, the lesions in some of the cases have been schematically represented on the surface of the cerebellum (Figs. 10-12). In general, the anatomical terminology of Larsell[4,5] (1937, 1947) has been used throughout.

CASE 1.—*A 41-year-old chronic alcoholic developed unsteadiness of gait, which was slowly progressive for two years, then stationary until death, at age 54. Repeated examinations demonstrated a*

Fig. 3 (Case 1).—Topography and intensity of cerebellar cortical lesions. Horizontal sections: (*1*) through upper medulla; (*2*) through midpons; (*3*) through upper pons.


1
2
3
MARKED NARROWING MOLECULAR LAYER, SEVERE LOSS PURKINJE CELLS, RAREFACTION GRANULE CELLS.
SLIGHT NARROWING MOLECULAR LAYER, SEVERE LOSS PURKINJE CELLS, GRANULE CELLS NORMAL.
MODERATE LOSS PURKINJE CELLS ONLY.

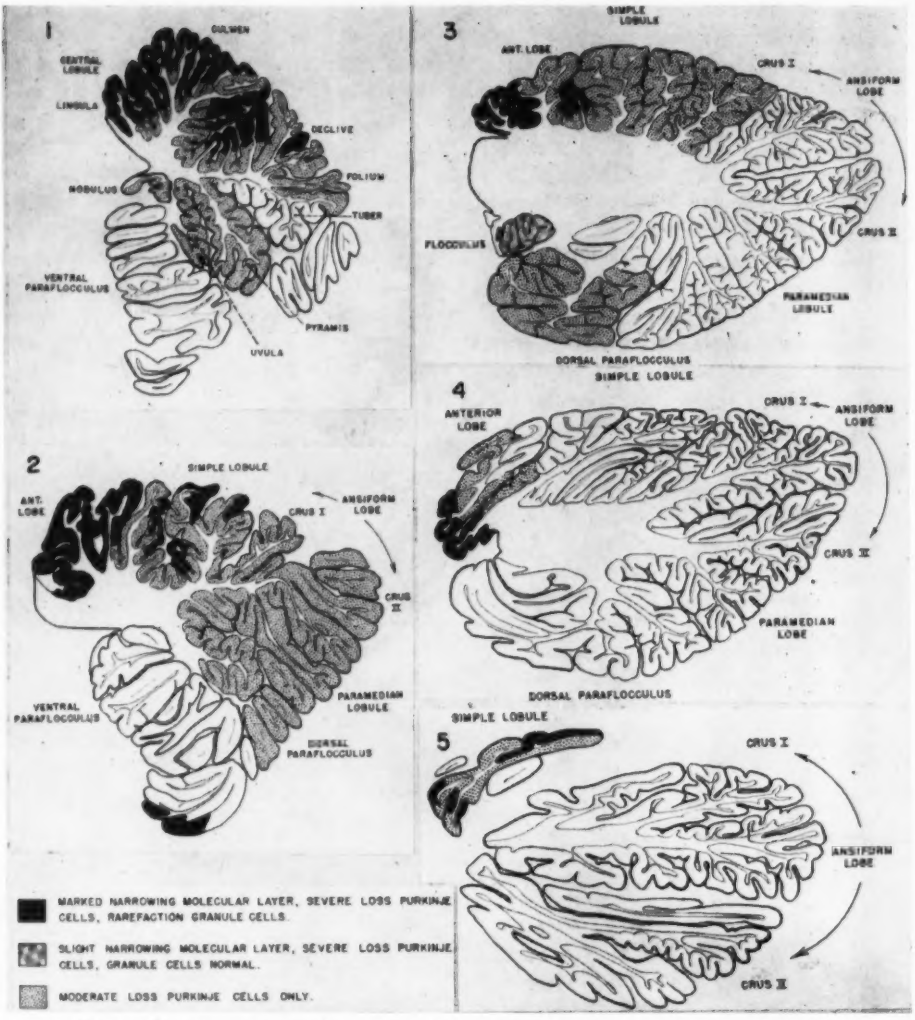


Fig. 4 (Case 2).—Topography and intensity of cerebellar cortical lesions. Sagittal sections beginning with vermis (*1*) and extending laterally through hemisphere (*2-5*).

severe cerebellar ataxia of gait and of the legs; arms were much less affected, and there was no nystagmus or dysarthria. Pathologically there was a symmetrical degeneration of all elements of the cerebellar cortex, severest in the vermis, the flocculi, the anterior lobes, and the paramedian portions of the simple lobules. There were also a nerve-cell loss and gliosis in the deep cerebellar nuclei, vestibular nuclei, and the olivary complex, and evidence of an old polyneuropathy and of Wernicke's encephalopathy.

Ad first came to our attention in 1950, at which time he was 50 years of age. His past and family histories were noteworthy only in regard to alcoholism. Both the patient's father and brother were serious alcoholics, and the patient himself was a confirmed drunkard by the age of 31. Toward the end of 1941, or perhaps early in 1942, he first noticed an unsteadiness of his legs, particularly when he climbed stairs. This disorder of gait was not severe in the beginning, and the patient continued to work as a taxicab driver, but he thought that it became slowly worse over the following 19 months or 2 years. Late in 1943 he was hospitalized elsewhere, following a period of unusually excessive drinking. Upon recovery from the

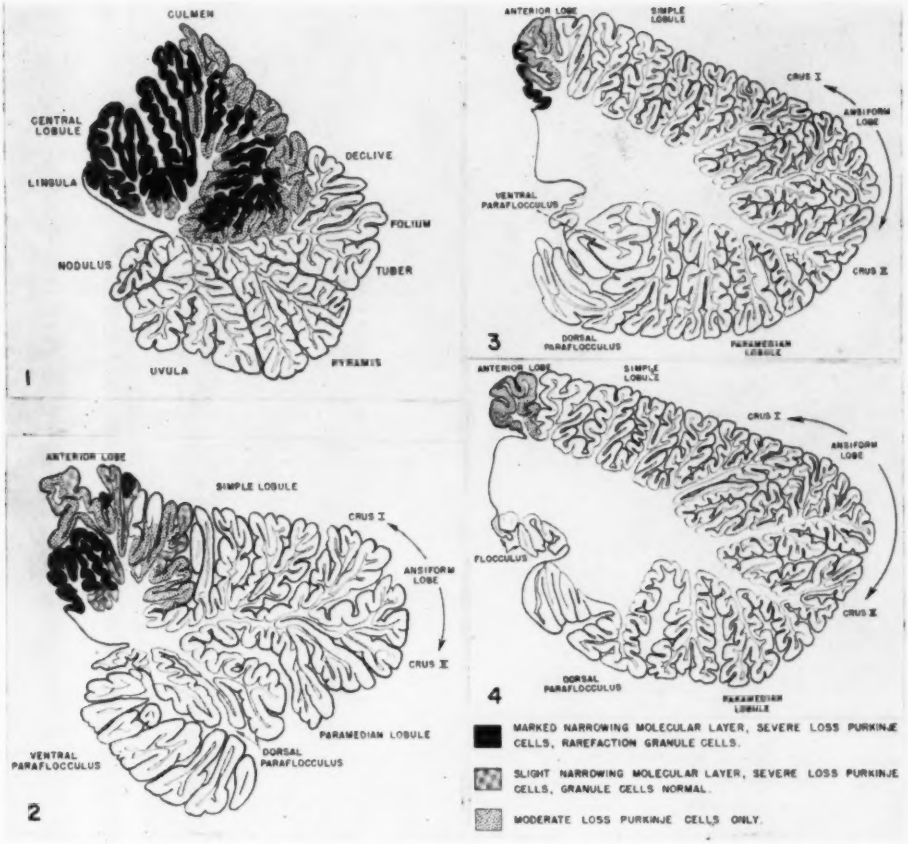


Fig. 5 (Case 3).—Cerebellar cortical lesions as seen in sagittal sections of vermis (*1*) and hemisphere (*2-4*).

symptoms of acute alcoholism, it became obvious that there was a severe ataxia of gait. From the clinical notes made on that occasion, it is also clear that there were no abnormalities of the arms in tests requiring precise movement, no dysarthria, and no evidence of polyneuropathy. A positive blood serology was noted at this time, but no lumbar puncture was performed; and, although the patient received antisyphilitic treatment, the amount could not be determined.

In the years which followed this hospitalization there was no significant improvement or worsening of his gait disturbance. However, there was some fluctuation of this disability, the ataxia being temporarily worse when he was drinking. His drinking thereafter was sporadic, with long periods of abstinence between individual drinking bouts. Between the years 1950 and 1954 the patient was hospitalized on five separate occasions, each in relation to such drinking sprees. The clinical findings, on repeated examinations, were much the same, and may be summarized as follows:

The liver was consistently palpable at the costal margin, and the testes were atrophic. The hair over the body and in the axillae was exceedingly sparse, and facial hair was limited to the chin and upper lip. The skin over the face was dry, sallow, and thickened; the teeth were carious, and in general his appearance betrayed an advanced state of personal neglect.

The patient was at all times alert and fully oriented, and there were never any overt indications of defective memory or of other cognitive impairment. Cranial nerve function was also normal; in particular, there was no nystagmus or dysarthria. He was able to walk alone, but on a wide base, with short, irregular steps, occasionally lurching to one side or another in an unpredictable manner. He watched his feet carefully as he walked, and his arms were held stiffly by his

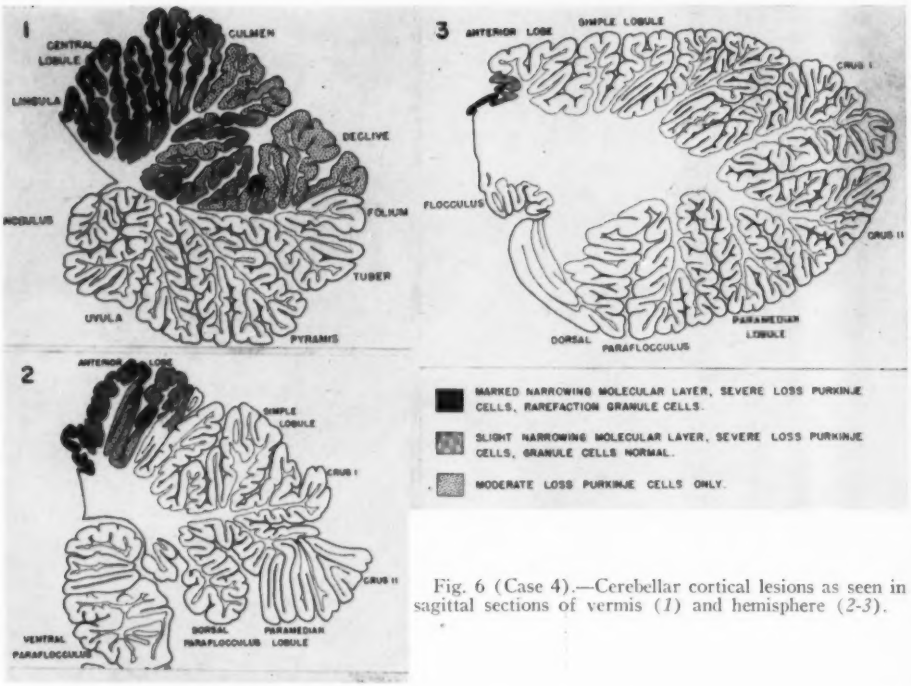


Fig. 6 (Case 4).—Cerebellar cortical lesions as seen in sagittal sections of vermis (*1*) and hemisphere (*2-3*).

sides, somewhat abducted. He was quite unable to walk a straight line. The ataxia was considerably worsened on closure of the eyes, turning, or trying to get into a chair. In performing these maneuvers, he required support to maintain his balance. There was a marked, typically cerebellar ataxia of the legs, best demonstrated by the heel-to-shin test. No distinct cerebellar ataxia or intention tremor in the arms could be demonstrated, although there was a slight rapid tremor of the outstretched hands, and the finger-to-nose test was carried out more slowly than normal. Rapidly alternating movements of the hands were well performed. The deep tendon reflexes were present and physiologically brisk in the arms but were depressed at the knees. The ankle jerks were barely obtained on some examinations and not at all on others. The plantar response was always flexor. Vibration sense was impaired in the legs, and position sense was slightly impaired in the great toes. There was a diminution of superficial sensation over the anteromedial aspect of both shins. Motor power and sphincter function were always considered normal. At no time was spasticity or hypotonia demonstrated.

Laboratory investigations, including examinations of the spinal fluid, were normal, with the exception of a persistently positive blood serology.

The patient's final admission to the hospital was in August, 1954. He was recovering from the effects of acute alcoholism, when he suddenly developed epigastric pain, abdominal distention, and paralytic ileus, followed shortly thereafter by peripheral circulatory collapse and death.

General Postmortem Findings.—The peritoneal cavity contained about a liter of dark blood. The gallbladder was ruptured, and there was evidence of recurrent cholecystitis. The heart weighed 460 gm.; there was some dilation and hypertrophy of the left ventricle and moderate atheromatous changes of the coronary arteries. The liver weighed 1,820 gm., and microscopically there was evidence of fatty metamorphosis.

Neuropathological Findings.—The brain weighed 1,480 gm. The cerebral hemispheres appeared normal except for a slight thickening of the leptomeninges. Coronal sections disclosed a persistent cavity of the septum pellucidum, but no other abnormalities. The lateral ventricles were of average size. The blood vessels were normal. The folia of the superior vermis and anterior lobes of the cerebellum appeared somewhat thin and the sulci widened (Fig. 13*A*).

Microscopic Findings (Figs. 3, 10).—The most striking changes were observed in the cerebellum, particularly in the cerebellar cortex and those

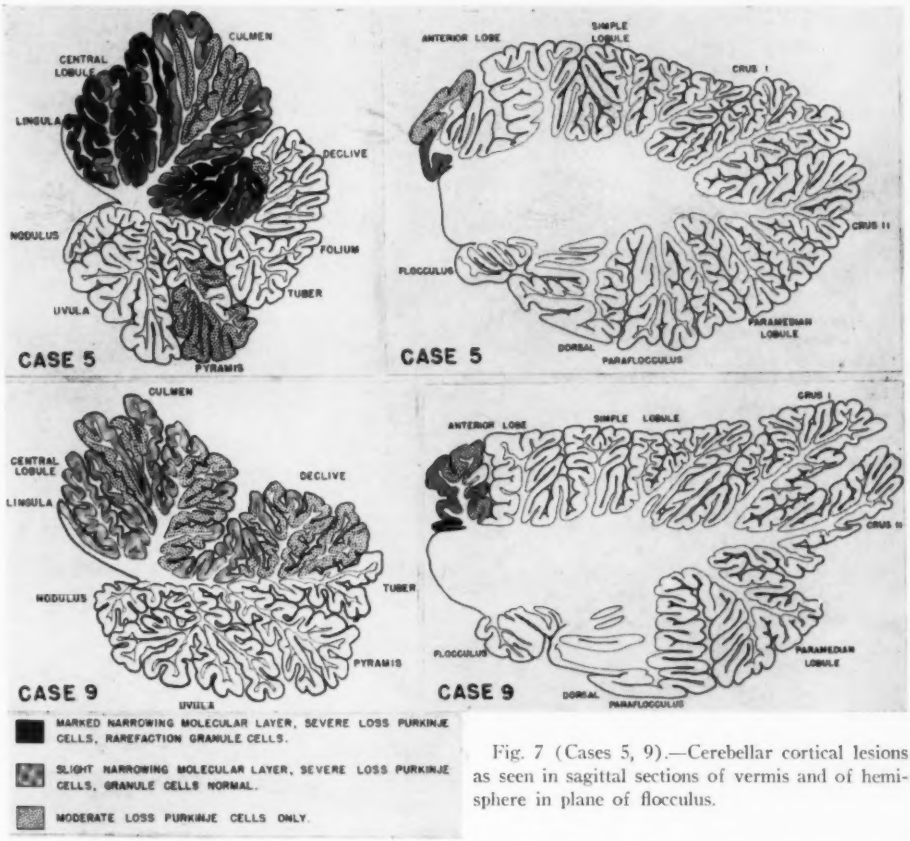


Fig. 7 (Cases 5, 9).—Cerebellar cortical lesions as seen in sagittal sections of vermis and of hemisphere in plane of flocculus.

structures with which it is connected. The most severely affected folia were in the *superior portion of the culmen*. Here, all elements of the cortex were markedly depleted. The Purkinje cells had entirely disappeared. The molecular layer was reduced to approximately one-third its normal width, and there was complete loss of the superficial stellate and basket cells. The granular cells were greatly reduced in number, and no Golgi II cells could be detected in this layer (Fig. 14*A*). Except for a rare remnant of a Purkinje cell (axis-cylinder "torpedo"), the cortical fiber systems had entirely disappeared, including the tangential fibers of the molecular layer, Purkinje-cell dendrites and recurrent axonal collaterals, climbing and mossy fibers, T-axons of the granule cells, and all pericellular baskets. Here and there some fat-laden macrophages could be found. There was an intense fibrous gliosis in this portion of the cortex; in places, in the atrophied molecular layer, a combination of these glial fibrils with adventitial fibrous-tissue reticulin formed striking glial-vascular whorls and tangles (Fig. 14*B*). The gliosis extended into the foliar white matter and diminished in intensity as the central white matter was approached. The myelin sheaths of the lamellar white matter were only slightly thinned.

Next most severely involved were the *flocculi*. Here, too, there was a severe loss of Purkinje cells, though a few of them could be found. Here, again, there was a marked atrophy of the molecular layer, with a reduction in the number of basket and superficial stellate cells. A patchy loss of granule cells had occurred, but Golgi II cells could still be detected (Fig. 15*A*). Gliosis, on the whole, was less marked than in the most heavily involved portion, and no glial-vascular whorls were seen. The deep tangential fibers of the molecular layer were relatively well preserved. Empty pericellular baskets were seen in large numbers, and they appeared coarse and heavily impregnated (Fig. 15*B*). The whole Purkinje-cell dendritic network was entirely lacking in some parts and was sparse in others, only rare thick-

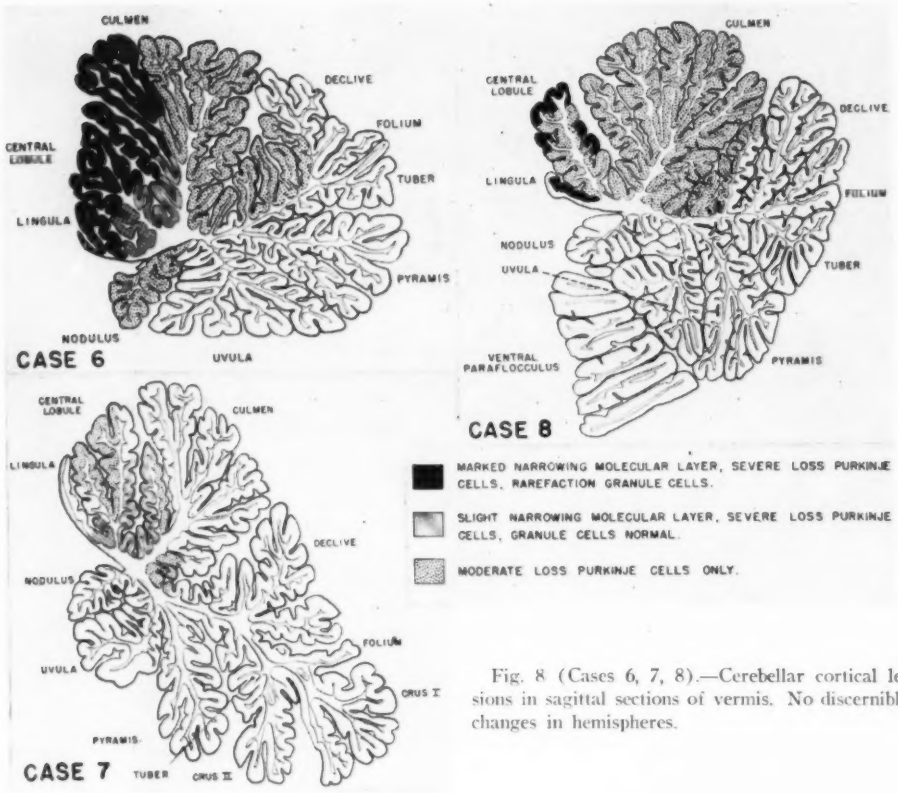


Fig. 8 (Cases 6, 7, 8).—Cerebellar cortical lesions in sagittal sections of vermis. No discernible changes in hemispheres.

ened axons being detected. Climbing fibers could not be identified with certainty, although a few delicate fibers, running vertically into the molecular layer and probably representing granule-cell axons, were visible. A scattering of fibers of fine caliber, probably representing mossy fibers, was also seen in the granular layer.

A somewhat less pronounced degree of involvement was evident in the *lingula, central lobule,* the *remainder of the culmen,* and the *declive, uvula,* and *superior pyramis,* as well as throughout both *anterior lobes* and the *paramedian portions of the simple lobules.* In these regions, most of the Purkinje cells had disappeared completely (Fig. 16*A*). Rarely, a relatively normal-appearing cell of this type was found. Here and there, darkly staining, shrunken pyknotic cells were present; they were thought to be Purkinje-cell remnants, on the basis of their location. A few very pale and occasional globular nerve cells also persisted; these cells showed a number of changes of uncertain significance, viz., eccentricity of nuclei, indistinctness of nuclear and cytoplasmic boundaries, and loss of the usual Nissl pattern. The Nissl substance was represented either by a fine basophilic powder, scattered throughout the cytoplasm, or by a few large blocks confined to the perinuclear region. The molecular layer in these zones was narrowed to about half the usual width, and was actually more cellular than normal, owing to the large numbers of small astrocyte nuclei (Fig. 16*A*). The superficial stellate and basket cells were of natural appearance and were present in their usual number. The Bergmann glia cells were strikingly proliferated, and there was an increase in number and thickness of the radially oriented Bergmann glia fibrils (Fig. 16*B*). The dendritic processes of the Purkinje cells were totally lacking, as would be expected, and only a rare thickened axon could be seen. The deep tangential fibers of the molecular layer appeared somewhat less numerous than usual, perhaps owing to the loss of the recurrent collateral fibers of the Purkinje-cell axons. The peri-Purkinje basket formations were generally preserved; but many of them had collapsed, and their fibers were impregnated rather coarsely and irregularly. Occasionally, such a "thickened" basket

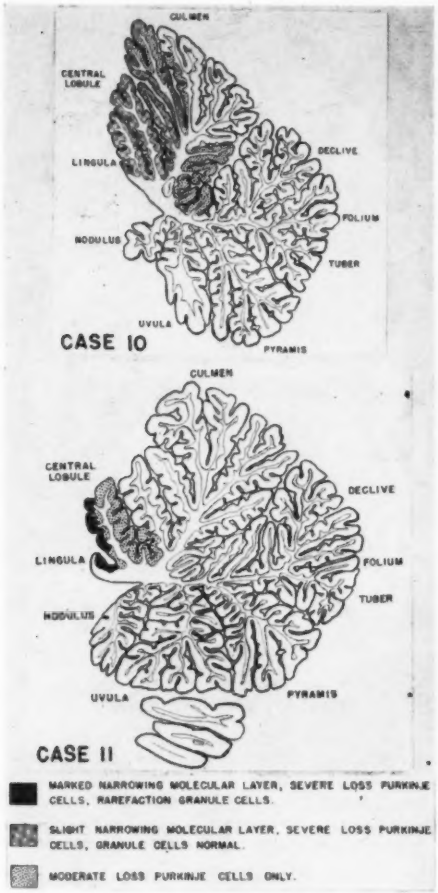


Fig. 9 (Cases 10, 11).—Cerebellar cortical lesions in sagittal sections of vermis. No pathological alterations in hemispheres.

was found around a surviving Purkinje cell. Fibers ascending from the granular into the molecular layer (T-axons of the granule cells and climbing fibers) were identifiable, but were perhaps less numerous than normal. Over large segments of the granular layer there was pallor of staining, but no definite loss of the granule cells or of the stellate cells (Golgi II) could be discerned. There was mild proliferation of astrocytic nuclei in this layer. Again, the mossy fibers could not be identified with certainty, but a number of fibers of fine caliber were visible in the granular layer, occasionally aggregating into stellate clumps. There appeared to be less of these fibers than in parts of the cerebellar cortex which were otherwise normal. Myelin stains demonstrated a mild degree of pallor of the lamellar white matter, and here also there was moderate proliferation of plump astrocytic nuclei.

In the *folium, tuber, posterior pyramis,* and *nodulus,* as well as in the more *lateral portions of the simple lobules* and in the *dorsal paraflocculi,* there was a moderate loss of Purkinje cells. There were a few scattered pyknotic remnants and many pale forms, with the cytological characteristics already described. The molecular layer was only slightly narrowed, and there was only a minimal increase of astrocytic nuclei. Bergmann glial cells were proliferated to only a slight degree. The granular layer was considered completely normal, and there were no convincing changes in the underlying white matter.

In the remainder of the cerebellar cortex, i.e., in the *ansiform* and *paramedian lobules* and the *ventral paraflocculi,* there was no loss of Purkinje cells, although the qualitative cytological changes of uncertain significance were again much in evidence. The molecular and granular layers were entirely normal; there was no gliosis.

It should be added that throughout the involved areas of the cerebellar cortex the crests of the folia were generally more severely affected than the depths.

There were definite thinning and pallor of the myelinated fibers in the *floccular peduncles,* with attendant mild gliosis; apart from this, the central white matter of the cerebellum was normal (Fig. 17*C*).

Throughout the *dentate nuclei,* there was patchy loss of nerve cells and a moderate, diffuse gliosis. Many of the remaining nerve cells were pale, swollen, and filled with lipofuscin granules; a few were very pale and shrunken. There was a mild degree of pallor of myelin staining in the fleece and hilus of both dentate nuclei, with an accompanying proliferation of microglia cells and astrocytes. The *emboliform* and *globose nuclei* appeared shrunken; there was severe nerve cell loss and gliosis in these nuclei, as well as in the fastigial *nuclei.* The *medial* (direct) *fastigobulbar tracts* were quite pale in myelin-stained sections and were the sites of an intense fibrous astrocytosis. The uncinate bundles (hook bundle of Russell) showed no abnormalities.

Striking alterations had taken place in the olivary complex. There was a marked loss of nerve cells and severe gliosis in the medial portion of the dorsal laminae of the *inferior olives,* in all but the extreme lateral portion of the *dorsal accessory olives,* and in the posterior portions of the *medial accessory olives.* In the dorsal laminae of the inferior olives, the loss of nerve cells gradually shaded off laterally; the ventral laminae probably contained a normal number of nerve cells. Many of the remaining nerve cells of the olives were swollen, their nuclei being eccentric and their cyto-

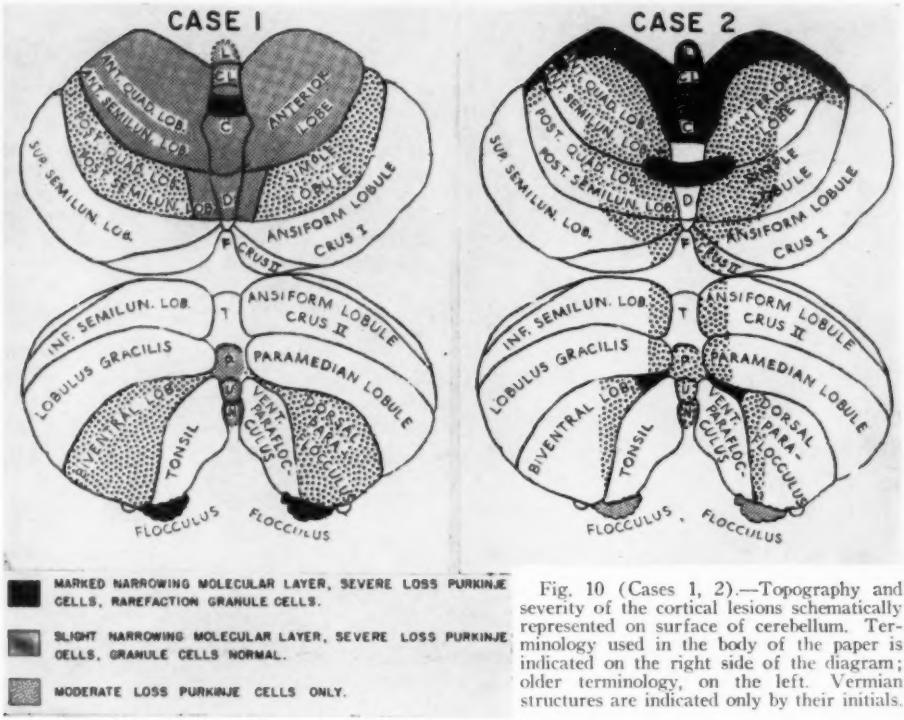


Fig. 10 (Cases 1, 2).—Topography and severity of the cortical lesions schematically represented on surface of cerebellum. Terminology used in the body of the paper is indicated on the right side of the diagram; older terminology, on the left. Vermian structures are indicated only by their initials.

plasm either vacuolated or stuffed with lipofuscin. There was no definite pallor of myelin staining in either the fleece or the hilus of the inferior olives, although a few abnormally thickened fragmented axis cylinders were visible in the hilus. There was no recognizable diminution in number of the olivocerebellar fibers in the medulla, but in the central portion of the restiform bodies there was a mild degree of pallor of myelin staining, with slight astrocytic proliferation.

A moderate proliferation of astrocytes and pleomorphic microglia cells was present in the *dorsal motor nuclei* of the vagus, but this change was not accompanied by a significant loss of nerve cells. The hypoglossal, external cuneate, and arcuate nuclei and the lateral and other reticular nuclei were normal, as were the nuclei of the columns of Goll and Burdach and the pontobulbar bodies. All the myelinated tracts within the medulla appeared normal. A slight but definite loss of nerve cells, with astrocytic gliosis, was present in the *spinal, medial, superior,* and *lateral vestibular nuclei.*

There was mild patchy loss of nerve cells in the *nuclei pontis.* Astrocytes were unusually prominent in some of the pontine nuclear masses and were more numerous where the nerve cells were thinned out. All fiber systems of the basis and tegmentum were normal, as were the *middle cerebellar peduncles* (Fig. 17*A* and *B*). The red nucleus was normal except for scattered groups of small- and medium-sized, pale, irregular astrocyte nuclei.

A variety of other changes were seen in the remainder of the nervous system. A small focus of ischemic necrosis was found in the right parietal lobe, and there was a slight prominence of astrocytic nuclei in the deeper layers of the cerebral cortex. The large pyramidal (Betz) cells were somewhat rounder than usual, and the Nissl substance was poorly staining, particularly toward the center of these cells. The central white matter and corpus callosum were normal. The caudate nucleus, putamen, and globus pallidus were normal except for a slight increase of irregular, pale, small astrocytic nuclei, particularly in the pallidum. In the *medial nuclei of the thalamus* there was a definite astrogliosis, and astrocytes were prominent in the subthalamic nuclei. There was a marked astrogliosis and a slight microglial proliferation in the structures bordering the third ventricle; these changes were particularly prominent 2-3 cm. lateral to the ependymal lining, but there was no definite nerve cell loss in the hypothalamic nuclei. There was total destruction of nerve cells, with

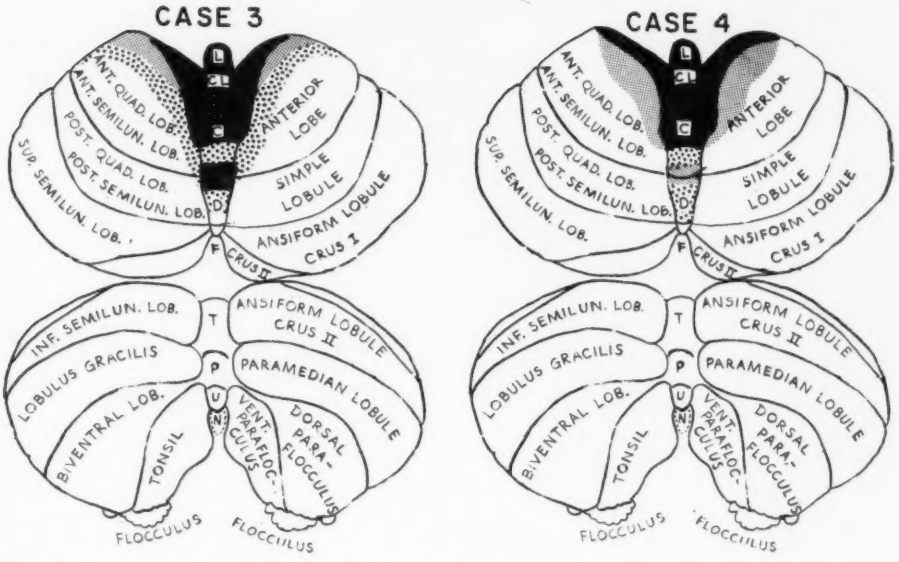


Fig. 11 (Cases 3, 4).—Schematic representation of cerebellar lesions, as in Figure 10.

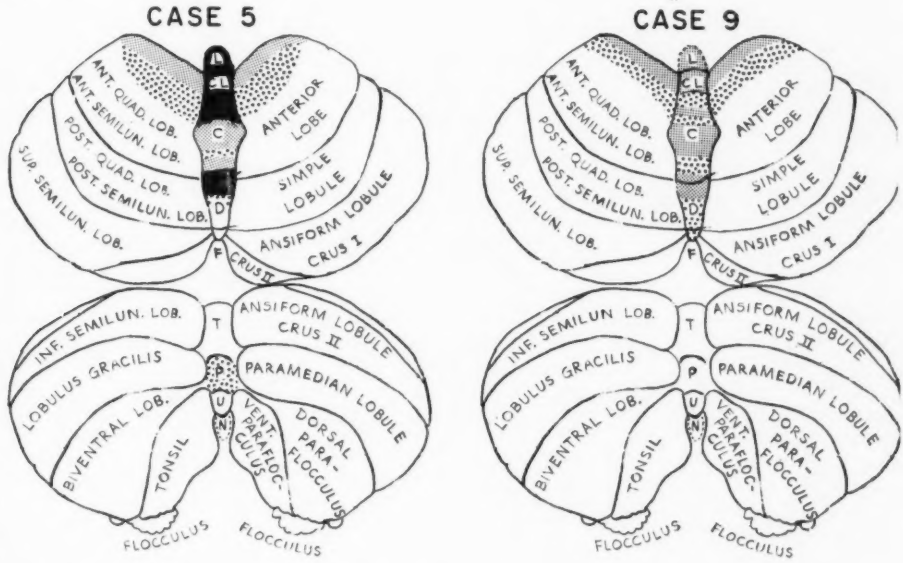


Fig. 12 (Cases 5, 9).—Schematic representation of cerebellar lesions, as in Figures 10 and 11.

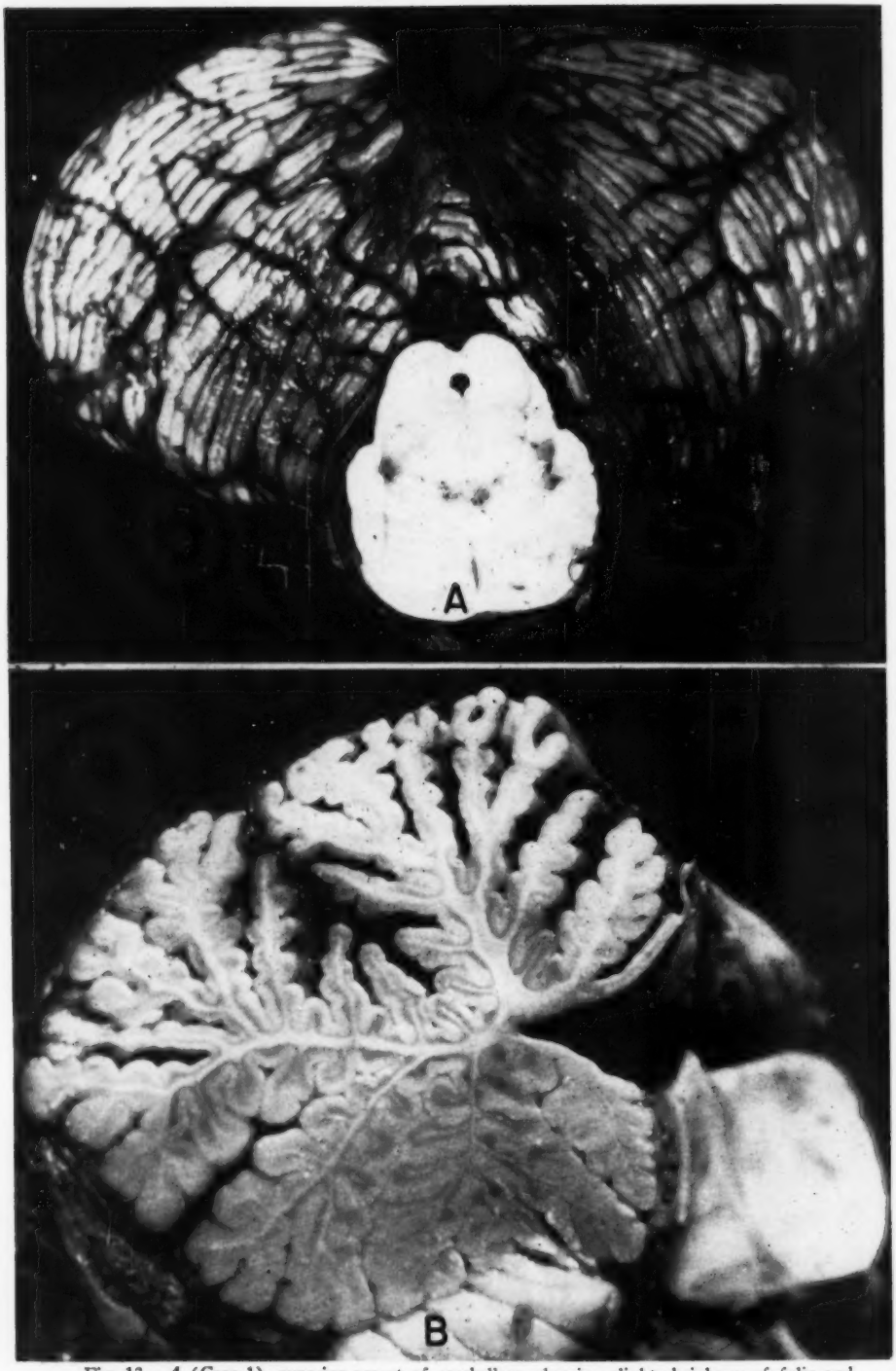


Fig. 13.—*A* **(Case 1)**, superior aspect of cerebellum, showing slight shrinkage of folia and widening of sulci of superior vermis, extending into most anterior portions of anterior lobes.

B (Case 2), midsagittal section of vermis. Shrinkage of folia and separation of superior vermis (lingula, central lobule, culmen, and portion of declive bordering on primary fissure). Inferior vermis appears grossly normal.

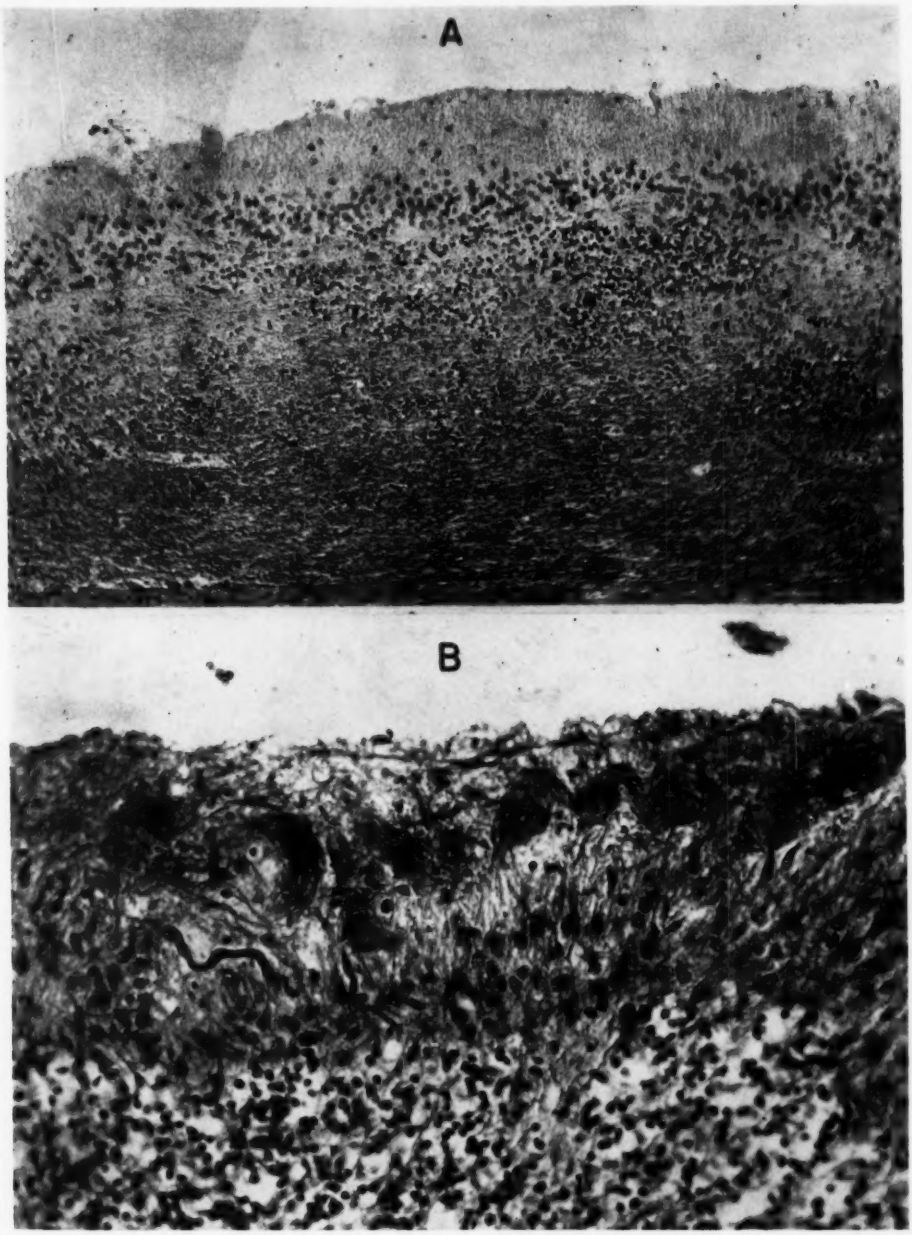


Fig. 14 (Case 1).—Culmen, illustrating the severest degree of involvement. *A*, marked narrowing of molecular layer, with loss of intrinsic nerve cells, absence of Purkinje cells, proliferation of Bergmann glia, and patchy loss of granule cells. Relative preservation of lamellar white matter. Oil red O stain.

B, intense fibrous gliosis and formation of glial-vascular whorls. Cajal reduced-silver method.

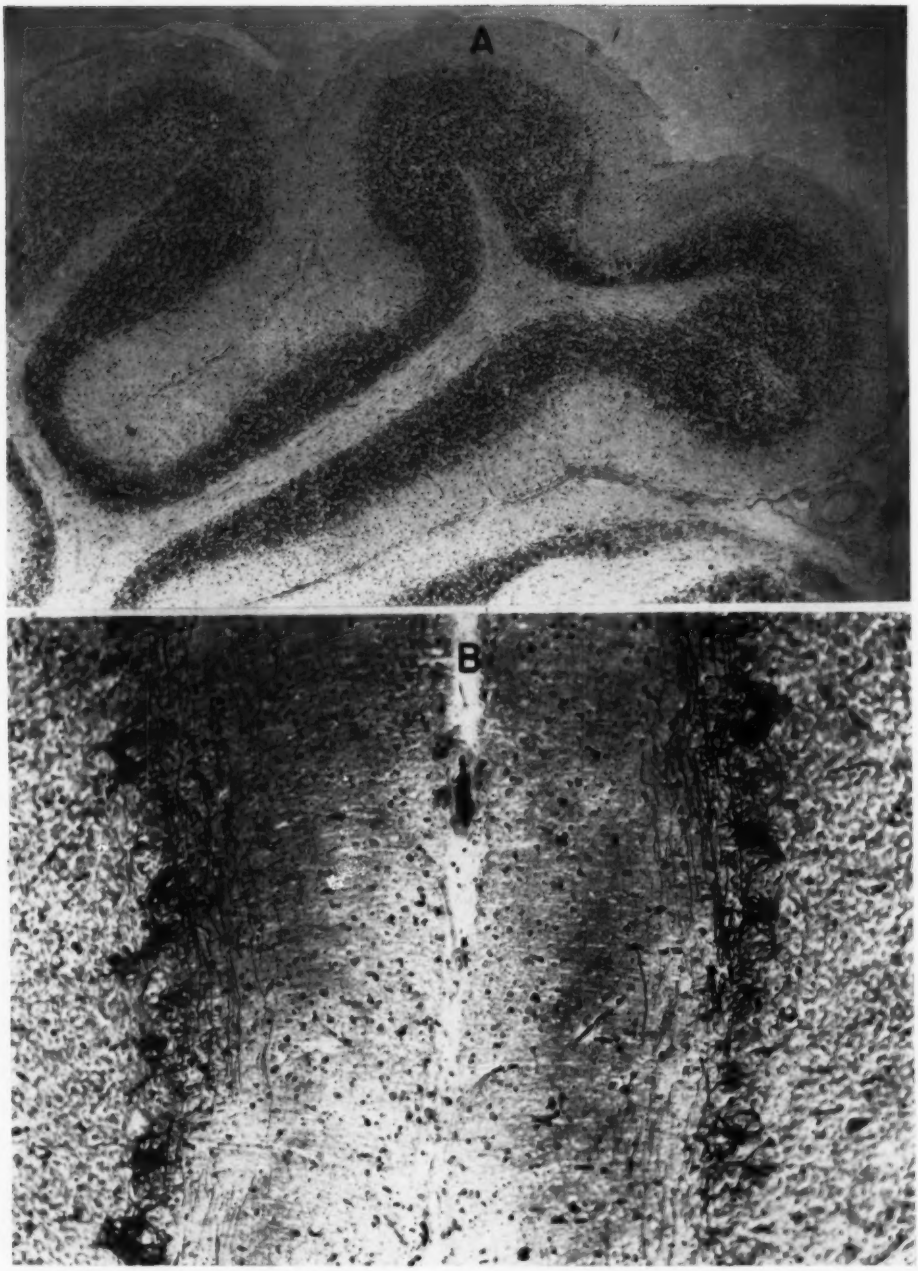


Fig. 15 (Case 1).—*A*, flocculus, demonstrating a somewhat less severe degree of affection than is shown in Figure 14. Narrowing of molecular layer, patchy loss of granule cells, and preservation of occasional Purkinje cell. The crowns of the convolutions are more affected than the depths. Cresyl violet stain.

B, preservation of some deep tangential fibers of molecular layer and heavily impregnated peri-Purkinje basket structures in moderately affected region (central lobule). Gros-Bielschowsky method.

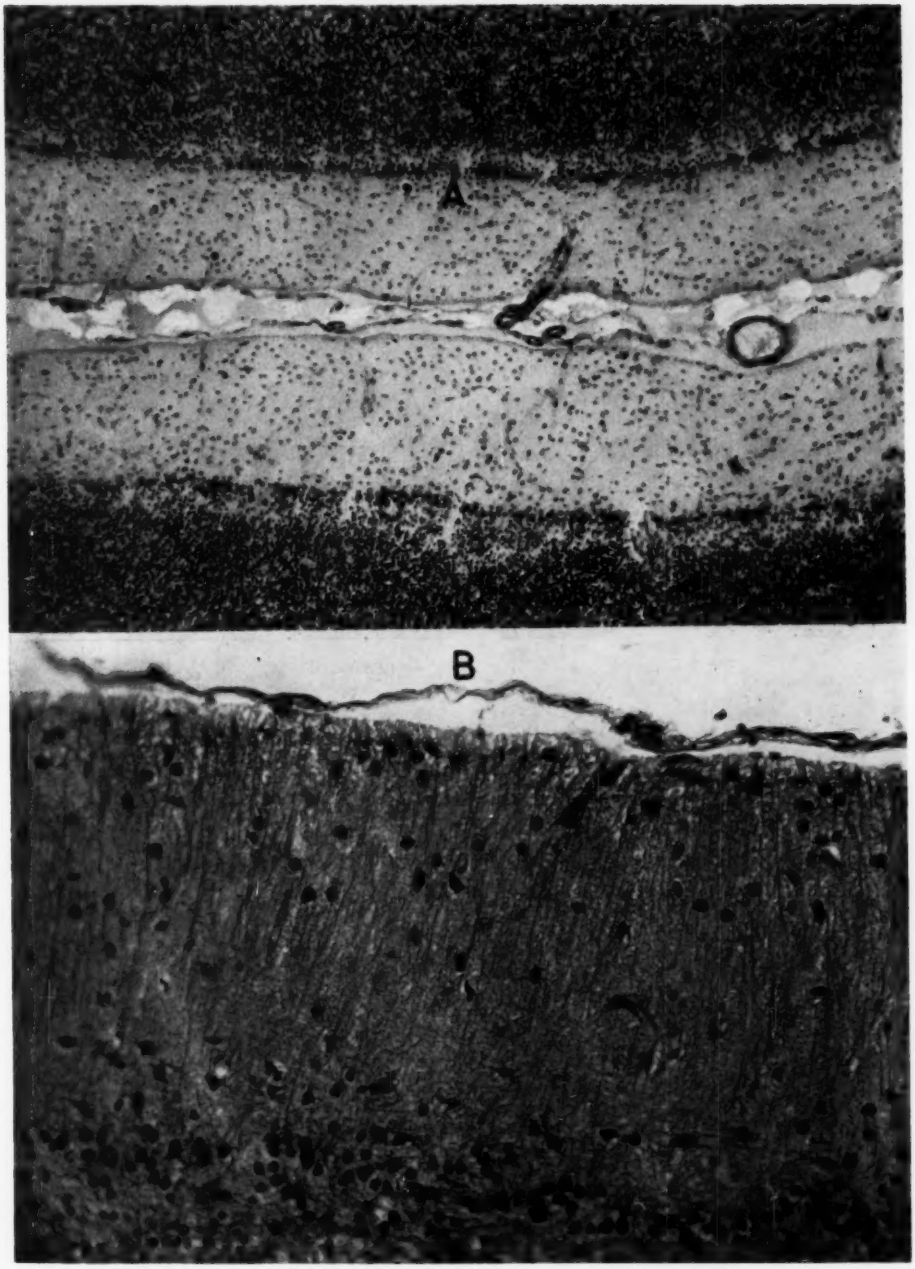


Fig. 16 (Case 1).—Central lobule. *A*, moderate degree of affection—slight narrowing of molecular layer, loss of Purkinje cells, proliferation of Bergmann glia, and preservation of granule cells. Cresyl violet stain.

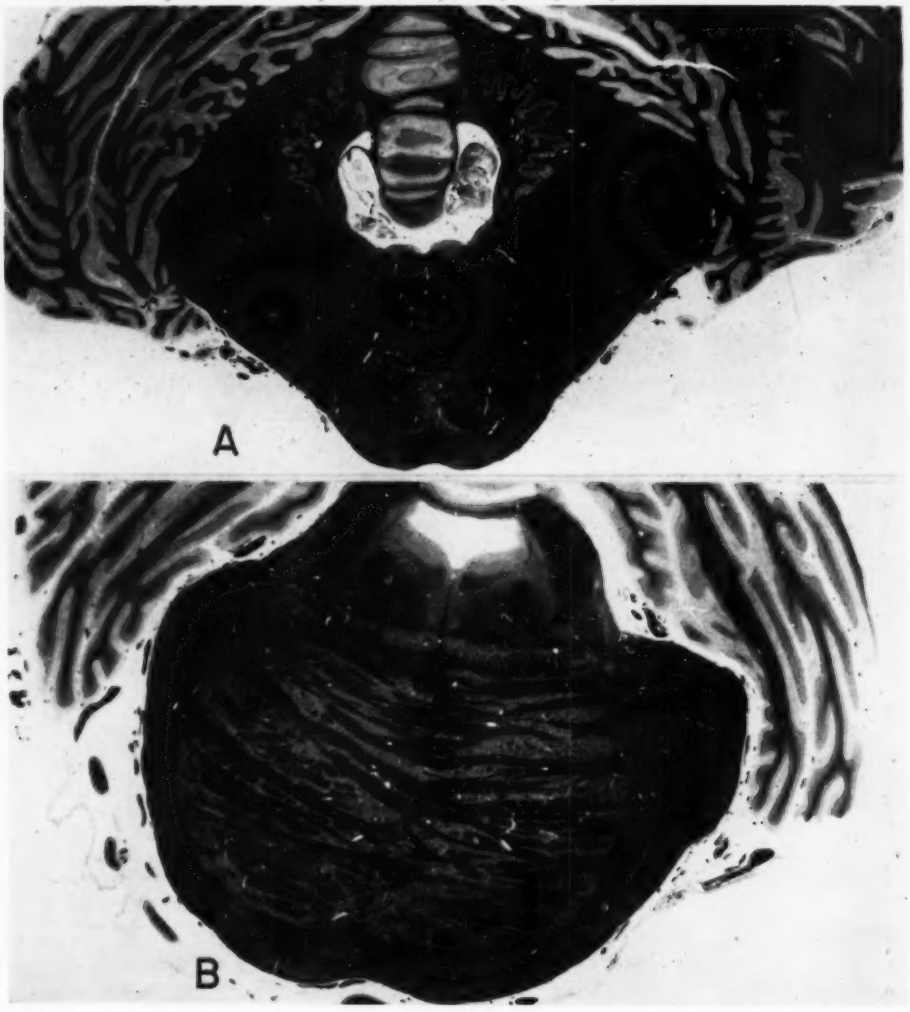
B, proliferation of radially oriented Bergmann glia fibrils. Phosphotungstic acid hematoxylin stain.

cavitation and gliosis in the central portions of the *mamillary bodies*; aside from some prominence of the endothelium, the blood vessels were not remarkable. The substantia innominata and supraoptic nuclei were normal.

In sections of the tibial nerves there were foci in which myelinated fibers had disappeared. No macrophages containing free fat could be found; there was some increase in fibrous connective tissue within the nerves. The walls of the small blood vessels were hyalinized. In the *spinal cord*, there was pallor in the posterior columns, most marked in the cervical segments, where the columns of Goll and Burdach were equally involved, the fasciculus proprius and fasciculus interfascicularis being spared. There was also a proliferation of small astrocytes in the posterior columns, with both isomorphic and anisomorphic gliosis. Several cells in the anterior horns of the lumbar segments of cord showed changes characteristic of secondary or "axonal" reaction.

Comment.—Clinically, this patient was typical of the group whose cerebellar symptoms progressed over a period of several years and then stabilized (Table 1, Group IIa). Pathologically, he represents the

Fig. 17 (Case 1).—*A* and *B*, sections through mid- and upper pons, showing integrity of middle and superior cerebellar peduncles, respectively. Loyez myelin stain.



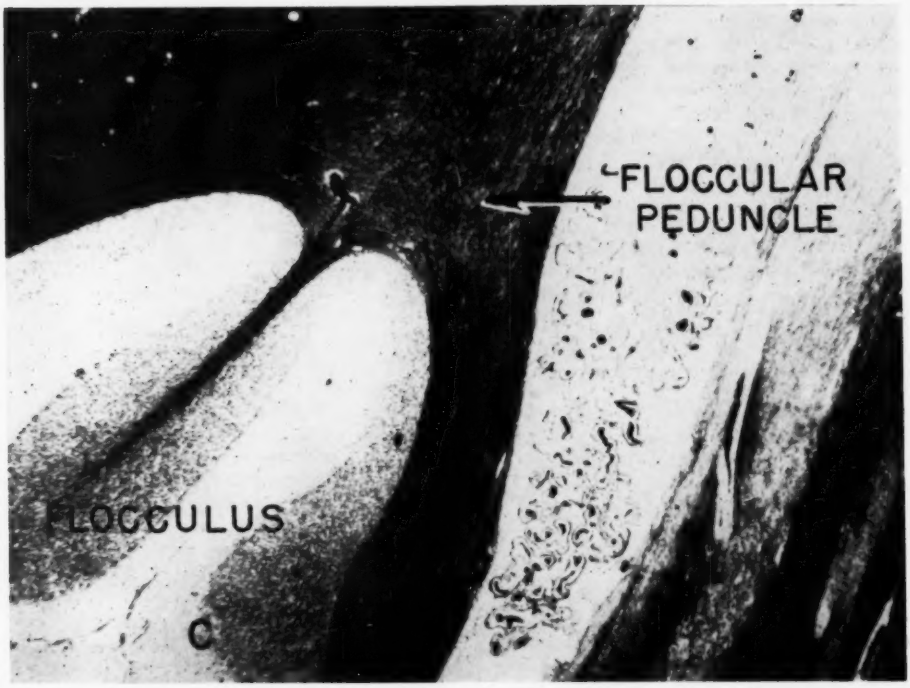


Fig. 17 (Case 1).—*C*, pallor of staining in floccular peduncle. Loyez myelin stain.

severest and most extensive example of this disease that we have observed.

CASE 2.—*A malnourished alcoholic woman developed a slowly progressive cerebellar syndrome, characterized by incoordination of gait and of the legs, relatively slight involvement of the arms, and nystagmus. Pathologically, in addition to advanced cirrhosis of the liver, a symmetrical degeneration of the cerebellar cortex was found, affecting the superior vermis and the paravermian and anterosuperior portions of the hemispheres most severely, and the flocculi to a less degree. Abnormalities were also present in the deep cerebellar, vestibular, and olivary nuclei.*

Ak, a 44-year-old housewife, was hospitalized for the first time in 1954, for the investigation of a gait disorder which had been present for five years. One day, at the age of 39, she found it necessary to hurry across a busy intersection and at that moment became aware of unsteadiness and poor control of her legs. The disorder of gait had been present ever since that episode, becoming gradually severer with the passage of time. The patient was able to get about without support except on certain occasions, particularly when she was emotionally distressed. Sporadic treatment with Multi-Vitamin capsules and injections of cyanocobalamin U.S.P. (vitamin B_{12}) had apparently not been beneficial.

There was a history of undoubted and grossly excessive drinking for at least 20 years, during which time the patient consumed as many as 20 Martini cocktails daily. During much of this time her dietary intake had admittedly been poor. Her past medical history was otherwise not remarkable, and there was no history of a similar disease or any other neurological illness in the patient's family.

General physical examination disclosed a moderate degree of hypertension (170/110). The limbs were emaciated, and the liver edge was palpable 3 cm. below the right costal margin. The other important abnormalities were found on neurological examination. The patient was unable to stand in the Romberg position, falling to either side if unsupported. She walked unsteadily with her feet placed wide apart; tandem walking was impossible. Heel-to-knee testing brought out a severe degree of incoordination of the legs. The arms did not appear to be involved; the finger-to-nose test was well performed bilaterally, and other movements were equally well coordinated. Cranial nerve function was intact, and, in particular, there was no

nystagmus or dysarthria. Motor power was considered adequate; the deep reflexes were physiologically brisk, and sensation was intact. There was no significant intellectual impairment. Ancillary examinations, including blood counts, urinalyses, "liver function" tests, and electroencephalography, disclosed no abnormalities.

Shortly after admission to the hospital the patient developed frank delirium tremens. She made an uneventful recovery from her delirium; but after leaving the hospital, she promptly reverted to her former drinking and dietary habits.

Three years later, in May, 1957, the patient was hospitalized again because of the gradual development, in the preceding months, of swelling of the abdomen and legs and of jaundice. Eight months before she had had a brief episode of hallucinosis. Examination at the time of the second admission demonstrated an advanced degree of icterus, ascites, and peripheral edema. The liver edge was palpable 4 cm. below the right costal margin and the spleen 3 cm. below the left costal margin. The gait was extremely ataxic, and the patient required constant support to stand and walk. Incoordination and dysmetria were now evident in the arms, as well as the legs, although the latter were much more severely affected. There was a mild horizontal nystagmus on gaze to either side; cranial nerve function was otherwise normal. There was no dysarthria. The tendon reflexes were intact, and there was no demonstrable sensory loss.

Laboratory investigations were consistent with the clinical signs of advanced cirrhosis of the liver. There was moderately severe normocytic anemia.

Soon after admission, the patient became confused and lethargic, and a "flapping tremor," characteristic of hepatic stupor, appeared. Her clinical course was complicated by the occurrence of gastrointestinal hemorrhages. Oliguria and uremia supervened; the patient lapsed into coma and died one month after admission, at the age of 47.

General Postmortem Findings.—There was a severe degree of icterus and ascites. The heart weighed 320 gm. but was otherwise normal. Both lungs showed bronchitis and focal atelectasis. The spleen weighed 220 gm. and was somewhat congested. The liver weighed 1,860 gm. The lobular pattern was completely distorted; there was fatty infiltration and destruction of parenchymal elements and some periportal fibrosis. Except for a small cortical adenoma of one adrenal, the endocrine glands were normal. The esophagus contained multiple varices, and there was considerable free blood in the stomach and small intestine.

Neuropathological Findings.—The brain weighed 1,200 gm. The leptomeninges were thin and transparent, and the large arteries were free of atheromatous change. The external appearance of the cerebral hemispheres was normal. Coronal sections demonstrated some dilatation of the lateral ventricles but no other abnormalities.

The cerebellum appeared slightly smaller than usual; after separation from the brain stem it weighed 105 gm. (formalin fixed). The cerebellum was sectioned sagittally. In the superior vermis the folia were shriveled and widely separated; this change involved the lingula, central lobule, culmen, and the part of the declive bordering on the primary fissure. The inferior vermis appeared grossly normal (Fig. 13*B*). Atrophy was also evident in the most anterior and superior folia of the cerebellar hemispheres.

Microscopic Examination.—The cerebellum was sectioned serially in the sagittal plane. A graded series of changes could be observed, symmetrically disposed in the vermis and through the hemispheres (Figs. 4, 10).

In the vermis, the *lingula, central lobule,* and *superior culmen* were the most severely affected; patchy involvement of equal intensity was present in the portions of the *culmen* and *declive* bordering on the primary fissure. Similarly, severe lesions were present in certain portions of the hemispheres—the *paramedian portions of the anterior lobes* and the *simple lobules* and in the medial portions of the dorsal paraflocculi. As in the first case, the involvement in these zones was not entirely even, areas of very serious involvement lying adjacent to areas less severely involved. In general, the crests of the folia tended to be involved more than the depths.

In these severely affected regions, all layers of the cortex were involved. The molecular layer was reduced to one-third or one-half its normal width and contained an increased number of small astrocytic nuclei. There appeared to be some reduction in number of the stellate and basket cells of this layer. The Purkinje cells were almost completely absent, but here and there a pale, shrunken cell was evident. The Bergmann astrocytes were markedly increased in number and size and often gave the appearance of a discrete layer separated from the underlying granule cells by a clear zone (Fig. 18*A* and *B*). Sections stained by the Holzer method demonstrated a similar degree of proliferation of Bergmann glial fibrils, extending perpendicularly through the molecular layer to the pial surface (Fig. 19*A*). Occasional small clusters of pleomorphic microglia cells and small astrocytes, suggestive of "glial bushes," were seen deep in the molecular layer. The number of granule cells was reduced, although the Golgi II cells of the granular layer were present in normal or near-normal numbers. A moderate degree of gliosis was present in the granular layer.

Silver-stained sections of these severely affected regions showed almost complete preservation of

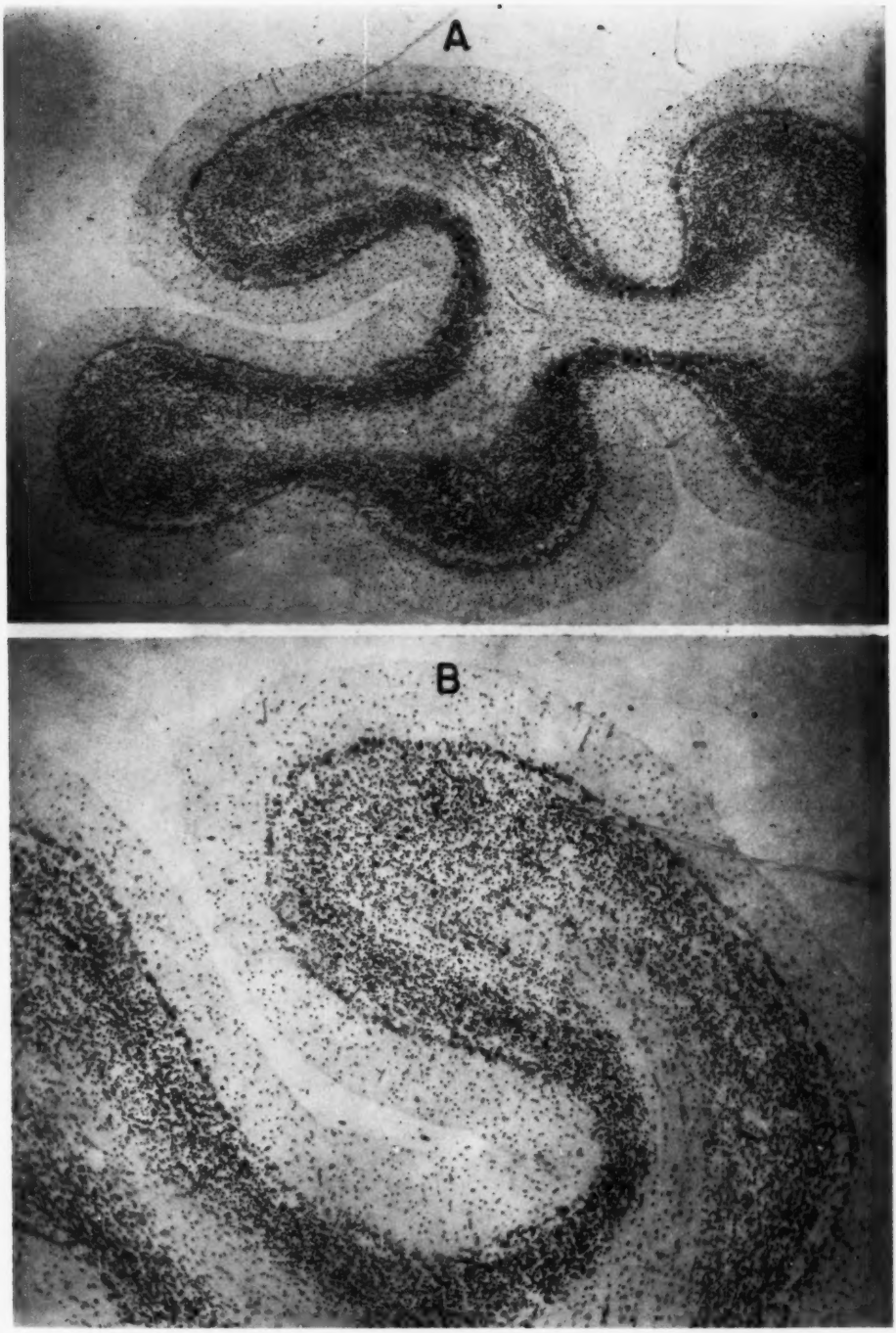


Fig. 18 (Case 2).—*A* and *B*, low- and high-power views of culmen, demonstrating severe degree of involvement, with shrinkage of molecular layer, increase in Bergmann glia, absence of Purkinje cells, and mild thinning of the granule layer. The increased cellularity of the molecular layer is due to proliferation of small astrocytic nuclei. Cresyl violet stain.

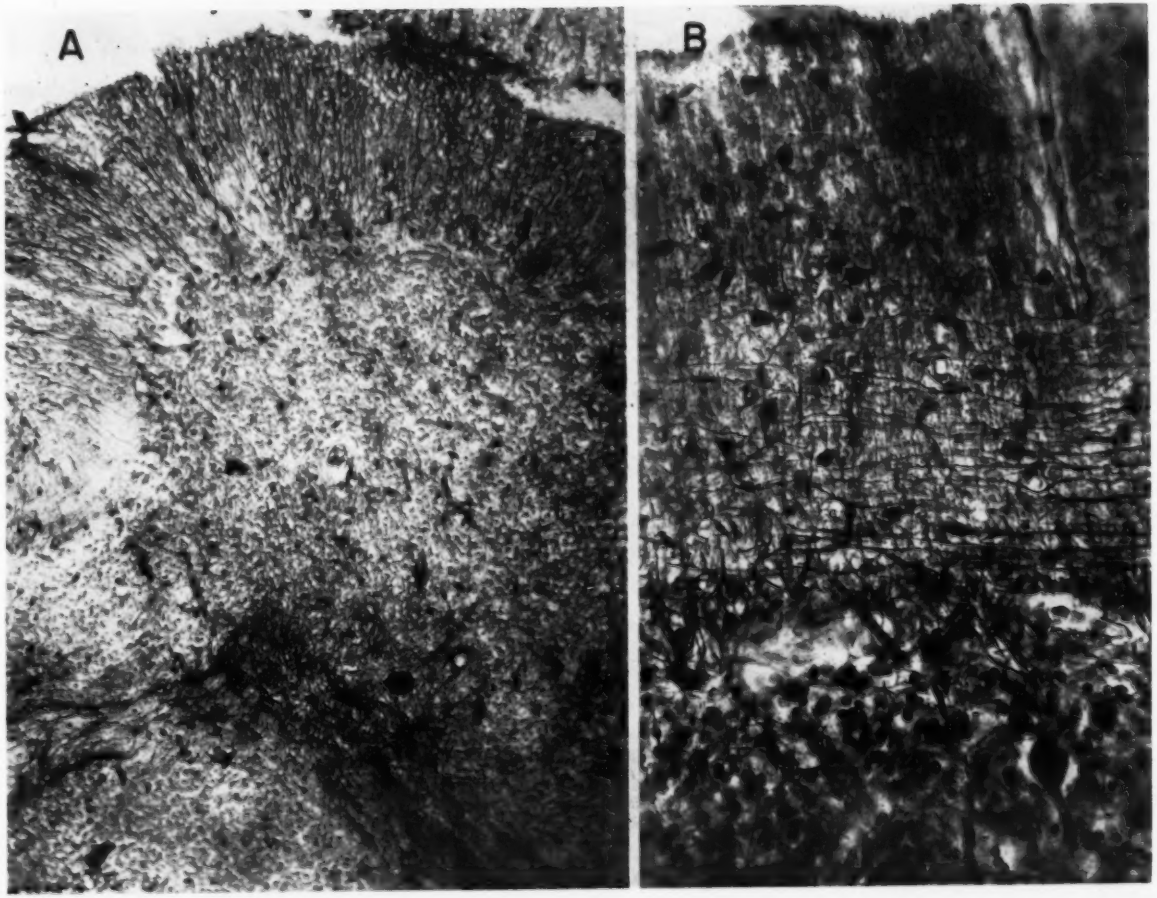


Fig. 19.—*A* (Case 2), section of culmen stained by Holzer method, showing marked proliferation of Bergmann glial fibers, extending perpendicularly through molecular layer to pial surface. There is also marked fibrous gliosis in the granule layer and lamellar white matter.

B (Case 3), central lobule, showing preservation of deep tangential fibers of molecular layer. Pericellular basket structures are empty but not thickened. Note the "axonal torpedo" (lower right). The difficulty in identifying various fibers of fine caliber in the granular and molecular layers is evident. Cajal reduced-silver method.

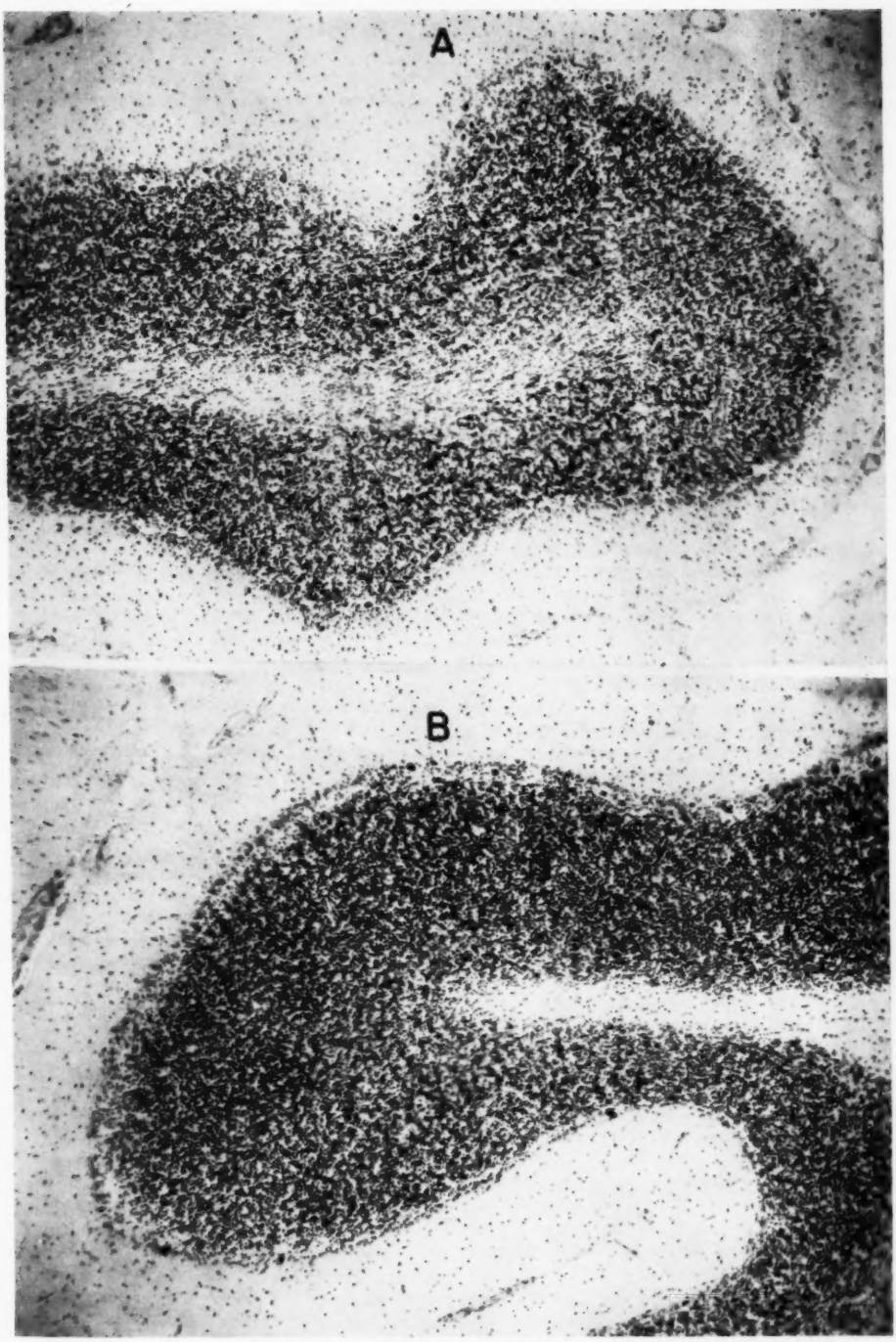


Fig. 20 (Case 2).—*A*, flocculus, showing uneven shrinkage of molecular layer, severe loss of Purkinje cells, and moderate proliferation of the Bergmann glia. The granular layer is probably normal. The degree of involvement is roughly comparable to that illustrated in Figure 16*A*. Cresyl violet stain.

B, uvula, demonstrating minimal degree of abnormality. There is a partial loss of Purkinje cells; the other components of the cortex are normal. Cresyl violet stain.

the pericellular basket structures, although most of them appeared collapsed and heavily impregnated. Tangential fibers of the molecular layer were generally preserved, but recurrent collateral fibers of the Purkinje-cell axons could not be found. Rare fragmented Purkinje-cell dendrites were present, but, for the most part, these cell processes were lost. A scattering of thickened Purkinje-cell axons was seen in the granular layer, and a rare axonal "torpedo." Occasional fibers, thought to represent climbing fibers, were identifiable; mossy fibers could not be identified with certainty, but there was an abundance of fibers of fine caliber in the granular layer. No significant number of fat-filled macrophages was seen. There was only a mild thinning of the myelin sheaths in the lamellar white matter. In contrast, intense fibrous gliosis was seen here, fading in intensity as the central white matter of the cerebellum was approached.

The *flocculi* were less heavily involved. Here the molecular layer was also shrunken, though to a less degree; and there was a slight proliferation of small astrocytic nuclei. The stellate and basket cells appeared intact. The loss of Purkinje cells was somewhat less marked than in the previously described regions; those which remained showed cytological changes of uncertain significance, e.g., elongated or globular forms, pallor and homogenization of the cytoplasm, eccentric placement of nuclei, shrinkage, and pyknosis. These cell forms often appeared to be displaced into the molecular or granular layer. Proliferation of the Bergmann glia was less pronounced than in the most severely affected portions. There was probably no reduction in the number of granule cells, and only a minimal gliosis in the underlying foliar white matter (Fig. 20*A*).

A minimal degree of affection of the remainder of the vermis was noted, except for the tuber, which was probably normal. The same minimal degree of abnormality extended through much of the *simple lobules, the remainder of the anterior lobes,* parts of the *dorsal paraflocculi,* and the *more superior paramedian portions of Crus I of the ansiform lobules.* In these regions the molecular and granular layers were normal. There was, however, a mild, though definite, reduction in the number of Purkinje cells (Fig. 20*B*). Many of those remaining showed the qualitative cytological changes already described. Gliosis was minimal. The rest of the cerebellar cortex (tuber, the remainder of the ansiform lobules and dorsal paraflocculi, and the paramedian lobules and ventral paraflocculi) showed no definite pathological changes.

The central white matter of the cerebellum was not affected in any way except for the *floccular peduncles.* In these bundles there was a moderate degree of pallor in myelin stains, accompanied by an intense fibrous gliosis.

The deep cerebellar nuclei showed a variety of changes. In the *dentate nuclei* there was an intense proliferation of pleomorphic microglia cells and astrocytes. These changes involved the most medial segments in their entirety, but in the lateral portions they were restricted to the anterodorsal segments. Most of the nerve cells in the affected portions of the dentate nuclei were darkly staining and appeared more closely packed than usual, but there was no obvious loss of these elements. Because of this difference in the number of glial nuclei and in the staining qualities of the nerve cells, the medial and anterodorsal portions stood out in sharp contrast to the remainder of the dentate nuclei. In the portions of the fleece and hilus of these nuclei which bordered on the areas of glial proliferation, a moderately dense fibrous glial meshwork was demonstrable with the Holzer stain, although the myelin sheaths appeared normal. In the remainder of the dentate nuclei the nerve cells were extremely pale, with yellow cytoplasm and eccentrically placed nuclei; there may have been a slight, patchy loss of these cells but no significant gliosis was detected, and the fleece and hilus in this region did not appear unusual. There was also a pronounced proliferation of pleomorphic microglia and astrocytes in the *emboliform, globose,* and *fastigial* nuclei, perhaps least severe in the latter. Nerve cells were definitely reduced in number in the emboliform, and perhaps in the other nuclei.

No definite changes were seen in the uncinate bundles or in the medial fastigiobulbar tracts.

In the olivary complex there was a loss of nerve cells with accompanying gliosis in the *inferior olives,* most marked in the medial portions of the dorsal laminae and diminishing in intensity laterally. The ventral laminae contained nerve cells and glial nuclei in the usual numbers. The *dorsal accessory olives* and the dorsal portions of the *medial accessory olives* were also the site of nerve-cell loss and gliosis, the former structure being more severely affected. In the abnormal regions of the olivary complex, the nerve cells which remained were extremely pale and often shrunken and distorted. In the more normal areas many of the cells contained so much lipofuscin that their nuclei were often pushed to one side. The hilus and fleece of the *inferior olives* showed a marked degree of pallor with myelin stains, and in the same areas the Holzer stain demonstrated a heavy gliosis. There was no obvious reduction in the number of olivocerebellar fibers, although there was a mild gliosis in this tract which extended into the restiform bodies.

A number of other abnormalities were found in the medulla. In the nucleus pallidus of the

raphe, nucleus gigantocellularis lateralis, and nucleus paragigantocellularis, widespread cell alterations suggestive of "axonal reaction" (swelling of the cell body, central chromatolysis, eccentricity of the nucleus) were found. The significance of these changes is uncertain, however, since at least some cells in these groups normally have such an appearance, according to Olszewski and Baxter.[6] Astrocytes were prominent in the hypoglossal nuclei and dorsal motor nuclei of the vagus. Aside from the myelinated fibers intimately connected with the inferior olives, the only other fiber systems of the medulla which were abnormal were the ventral spinocerebellar tracts. These exhibited marked pallor of myelin staining as they passed just superior to the postolivary sulci. Astrocytic nuclei were prominent here, and there was a minimal deposition of glial fibers. No fat-laden macrophages were to be seen.

No abnormalities were found in the paramedian reticular, lateral reticular, lateral cuneate, arcuate, or cochlear nuclei, or in the nuclei of the columns of Goll and Burdach. The so-called pontobulbar bodies were also normal.

The nuclei of the vestibular complex showed definite alterations. There was a partial loss of nerve cells, with marked proliferation of both astrocytes and microglia cells and a fibrous gliosis (as demonstrated by the Holzer stain) in the *spinal vestibular nuclei.* Glial nuclei were prominent in the *superior* and *lateral vestibular nuclei,* but there was no definite cell loss. The medial vestibular nuclei were normal.

In the pons several swollen cells, with an appearance of "axonal reaction," were seen in the motor nuclei of the trigeminal nerve, and there was an increased number of elongated microglia cells and astrocytes along the intramedullary course of the trigeminal nerve fibers. The tegmental structures were otherwise normal. The nuclei of the basis pontis were normal, although astrocytes with large nuclei and plump cell bodies appeared to be increased in number. A marked fibrous gliosis was present in the nucleus reticularis tegmenti (Bechterew), but there was no obvious cell loss. In addition, several small perivascular foci of total tissue necrosis were found in the basis pontis, with a cellular reaction consisting predominantly of pleomorphic microglia cells and fatty macrophages. The blood vessels were patent, and, aside from swelling of the endothelial cells, their walls were not unusual. The transverse pontocerebellar fibers and middle cerebellar peduncles were well myelinated, but contained a few large astrocytic nuclei, sometimes in pairs. The same was true for the superior cerebellar peduncle.

The nerve-cell population of the red nucleus, the substantia nigra, and the oculomotor nuclei were probably normal; slightly enlarged astrocytic nuclei were present in these nuclear groups, as well as throughout the tectum. A similar proliferation of pale, irregular, lobulated astrocytic nuclei of moderate size was seen in all portions of the basal ganglia, particularly in the thalamus and globus pallidus. In the mammillary bodies there was no definite nerve cell loss, although many of them appeared dark and shrunken. Here, also, there was a mild proliferation of astrocytes, and the endothelial cells appeared plumper than usual.

There was a patchy loss of nerve cells in the *cerebral cortex,* with the suggestion of a pseudolaminar distribution in the deeper layers. In these areas there was also a moderate proliferation of reacting astrocytes and rod-shaped microglia cells. The cell loss was most impressive in the hippocampal gyrus, where all layers were affected. In addition to the reactive glia in the regions of partial nerve cell loss, there was a diffuse proliferation of large, irregular pale astrocytic nuclei, often in pairs and groups. The convolutional and central white matter and the corpus callosum were normal.

The only important abnormalities in the spinal cord were in the columns of Goll, where pallor of myelin staining and fibrillar and cellular gliosis were in evidence. The abnormality of the spinocerebellar tracts, seen in the medulla, could not be traced into the spinal cord. The peripheral nerves were not available for examination.

The meninges were normal throughout, as were the blood vessels, with the exception of changes already noted in the basis pontis.

CASE 3.—*A seriously malnourished alcoholic man developed a cerebellar disorder of gait one year before his death, which resulted from delirium tremens and hepatic disease. Postmortem examination disclosed a symmetrically distributed degeneration of the cerebellar cortex in the superior vermis and the anterior parts of the hemispheres. The olives and vestibular and deep cerebellar nuclei were also involved.*

R, a 54-year-old investment broker, was admitted to the hospital in March, 1958, suffering from delirium tremens. The patient's father had been addicted to alcohol, and since early manhood alcoholism had also been a grave problem to the patient. With the exception of occasional interruptions, lasting only several weeks or a month, he drank steadily and in gradually increasing amounts, so that for five years before his death he was drinking 25-30 oz. of whisky daily. During this last period his diet was grossly defective—he rarely ate breakfast; lunch was meager, consisting as a rule of a bowl of soup, and his wife could hardly recall an occasion on which he ate an adequate dinner.

During this period of greatly excessive drinking, a number of serious illnesses, attributable both to alcoholism and to malnutrition, had occurred. There

were several episodes of tremulousness and transient hallucinosis when he tried to abstain from alcohol. In the summer of 1955 his vision deteriorated over a two-month period, and examination disclosed the presence of a centrocecal scotoma in each eye; the visual acuity improved temporarily with the parenteral administration of B vitamins. In March, 1957, he was hospitalized for an attack of tremulousness and hallucinosis; ocular examination at this time showed that his visual acuity had again deteriorated and that there was evidence of primary optic atrophy.

After this hospitalization, he reverted immediately to his previous alcoholic and dietary habits. Shortly afterward a staggering gait was observed for the first time. The abnormality of gait did not worsen perceptibly over the ensuing year, despite the fact that over this period he continued to drink steadily, and even more than before. At first, the staggering was attributed to intoxication, but it soon became obvious that it was present even when he was sober. The patient walked with his feet set wide apart, his trunk pitched slightly forward, with his eyes fixed on the ground before him. He required support on walking down the stairs or in seating himself. The coordination of his arms and his enunciation of words were apparently unaltered.

The patient's final admission to the hospital was in March, 1957. He was in a state of profound confusion, characterized further by vivid hallucinations, constant wakefulness, and ceaseless speech, psychomotor and autonomic overactivity. A detailed neurological examination was precluded by the state of continued agitation, but it could be determined that there was no nystagmus or other oculomotor disorder. The deep reflexes were present in the arms but absent in the legs, and the plantar reflexes were flexor. The spinal fluid was normal. The course of this delirium was complicated by fever, the development of aspiration pneumonia, and hepatic failure with deepening jaundice; and he died five days after his admission to the hospital.

General Pathological Findings.—The main abnormalities were in the lungs and liver. The left lung was entirely consolidated, and the lower lobe contained several confluent abscesses filled with creamy pus. A patchy bronchopneumonia was present in the right lung. The liver weighed 2,040 gm. and was firmer than normal. The surface was dark orange-yellow in color and granular. Microscopically, there was a severe vacuolation of the liver cells, mainly adjacent to and involving the central areas, and a slight increase of portal fibrous tissue.

Neuropathological Findings.—There was a moderately severe degree of convolutional atrophy in the frontal regions, with slight thickening and opacity of the overlying pia-arachnoid. A slighter degree of convolutional atrophy was probably present throughout the remainder of the cerebral hemispheres. Coronal sections through the cerebral hemispheres showed a mild degree of enlargement of the lateral and third ventricles. Otherwise, there were no gross abnormalities.

The cerebellum appeared to be of normal size and, after removal from the brain stem, weighed 130 gm. On inspection of the intact cerebellum the convolutions of the superior vermis appeared somewhat shrunken, but this became strikingly evident when the vermis was divided sagittally. This shrinkage was confined to the lingula, central lobule, much of the culmen, and the part of the declive bordering on the primary fissure (Fig. 21*A*). The sulci gaped widely in these atrophic regions, and the overlying meninges were slightly more opaque than usual. The remainder of the vermis appeared normal.

Microscopic Findings. — The cerebellum was studied in serial sections in the sagittal plane (Figs. 5, 11). The significant changes in the cerebellar cortex were confined to the superior vermis and anterior portions of the hemispheres. Most severely affected were the *lingula, central lobule, culmen,* the *portion of the declive in the depths of the primary fissure,* and the *dorsal portion of the paravermian aspect of the anterior lobes* (Fig. 22*A*). As in Cases 1 and 2, the depths of the folia were in general less affected than the remaining portion. Another noteworthy feature within the region of severe involvement was the patchy manner in which some of the folia, particularly in the culmen and superior declive, were involved. The transition from a severely to a less severely involved part could be remarkably abrupt. The molecular layer was reduced to one-third or one-half its normal width. In this layer the superficial stellate and basket cells were reduced somewhat in number; in places there was a slight increase in small astrocytic nuclei and microglia. A marked reduction in the number of Purkinje cells was noted, and many of those remaining were small and chromatolyzed, with only perinuclear accumulations of Nissl substance remaining. A few microglia containing fine sudanophilic material was seen. There were hypertrophy and mild hyperplasia of the astrocytes in the Purkinje-cell layer. However, with the Holzer stain a marked increase in the vertically oriented glial fibrils in the molecular layer could be demonstrated. This glial overgrowth was particularly intense in the subpial region. In addition, there were some small aggregates of pleomorphic microglia cells and small astrocyte nuclei, suggesting "glial bushes." There was a definite reduction in granule cells, and many of the remaining ones were pale. The Golgi II cells of the granular layer were probably slightly reduced in number.

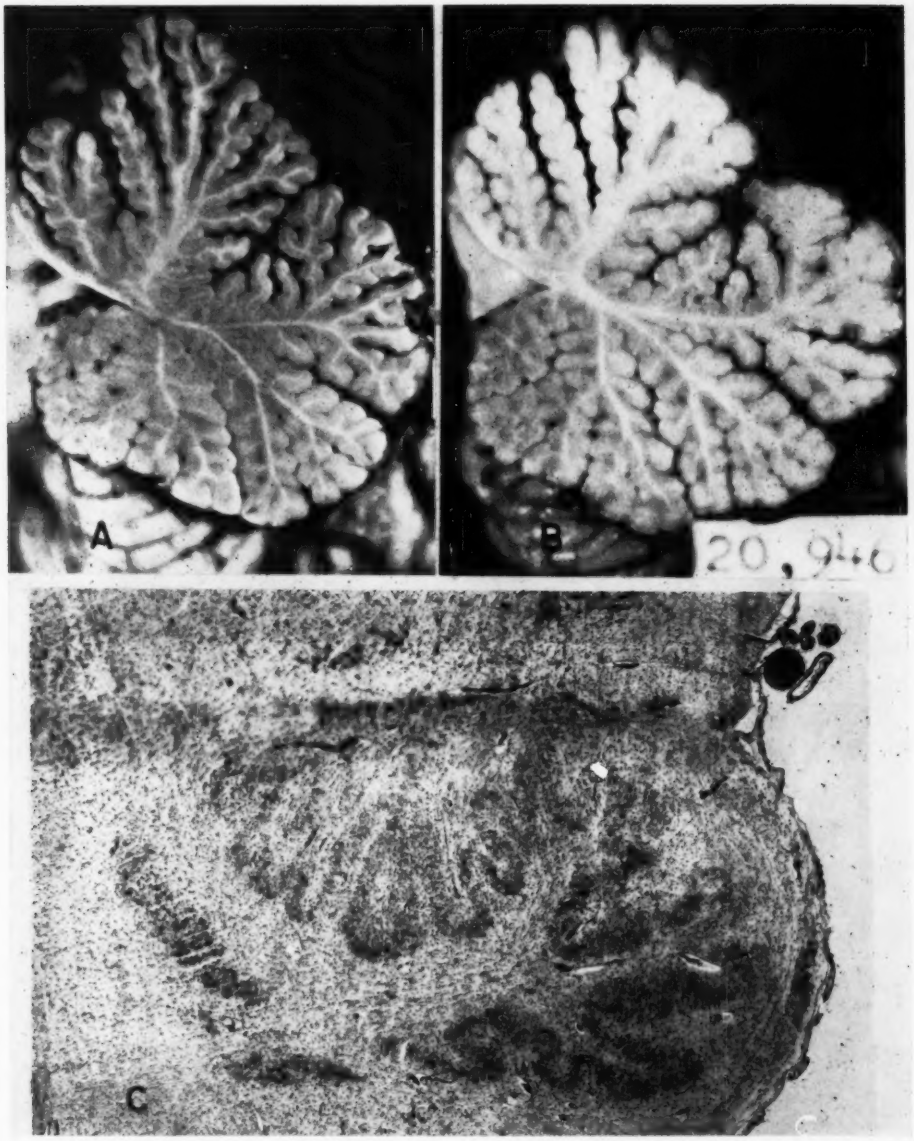


Fig. 21.—*A* (Case 3), midsagittal section of vermis, showing characteristic shrinkage of folia of superior vermis. This change is virtually identical with that illustrated in Figure 13*B*.
B (Case 4), less severe degree of affection of superior vermis.
C (Case 5), low-power view of olivary complex, showing loss of nerve cells and gliosis in dorsal lamina of inferior olive, most intense medially. There is also some loss of nerve cells in the dorsal portion of the medial accessory olive. The severe nerve-cell loss and gliosis in the dorsal accessory olive are not well shown. Cresyl violet stain.

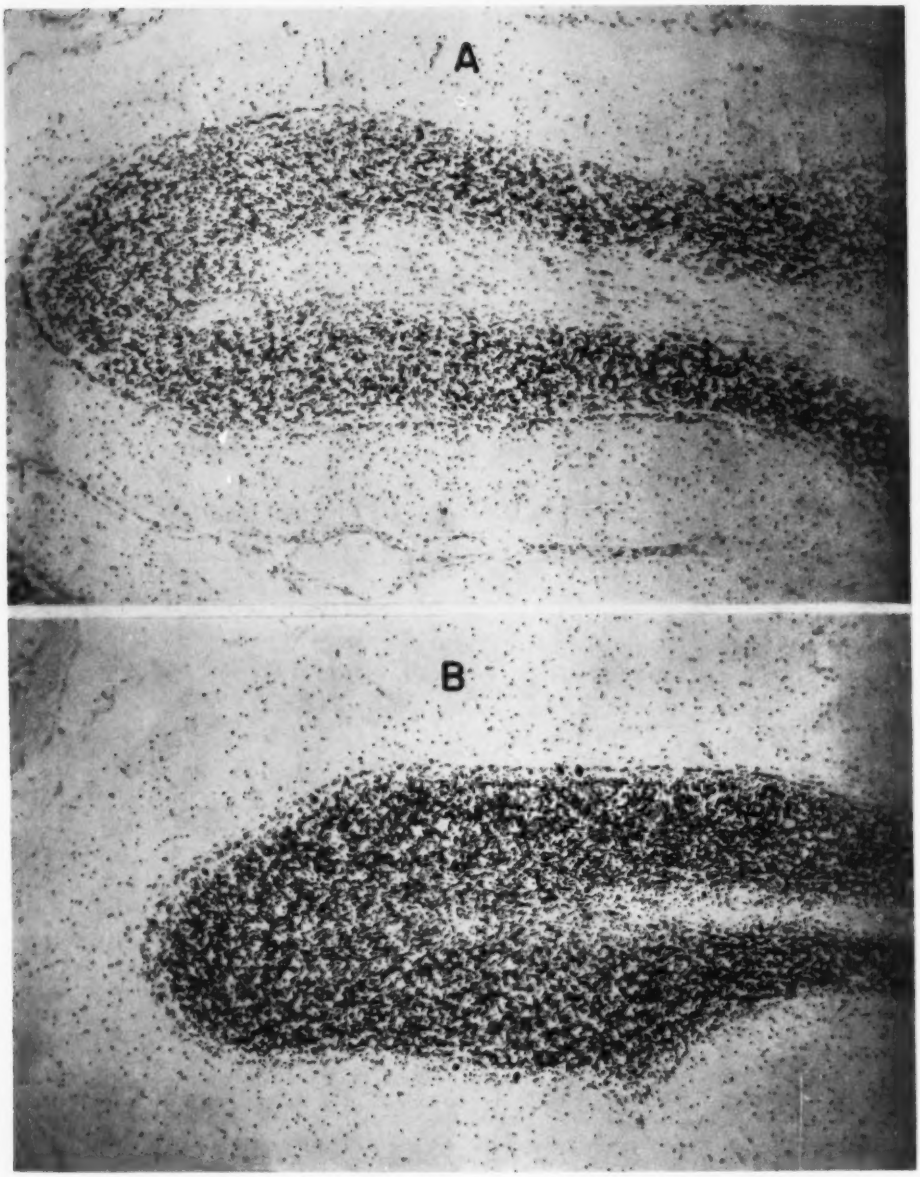


Fig. 22 (Case 3).—*A*, lingula, demonstrating a severe degree of affection of all neurocellular elements of the cortex. The involvement is most prominent at the crests of the folia. Cresyl violet stain.

B, anterior lobe, demonstrating less severe degree of affection. Cresyl violet stain.

The deep tangential fibers of the molecular layer were well preserved. Empty and collapsed pericellular baskets were numerous; their constituent fibers were not thickened. Some fragmented Purkinje-cell dendrites were seen, and also rare swollen Purkinje-cell axons in the form of "torpedoes" (Fig. 19*B*). A scattering of fibers running vertically from the granular into the molecular layer was also seen; these fibers probably represented both climbing fibers and granule-cell axons. The fine-caliber fibers of the granular layer (probably the mossy fibers) were not perceptibly reduced. The lamellar white matter showed a mild pallor of myelin staining and a minimal degree of thinning of nerve fibers. In contrast, there was an intense fibrillar gliosis, with some increase in astrocytic nuclei. This gliosis tended to diminish as the central white matter of the cerebellum was approached.

A less severe degree of involvement of the cerebellar cortex was present in the *remainder of the paramedian portion of the anterior lobes* (Fig. 22*B*). As one proceeded laterally, the changes in the anterior lobes became less intense and progressively more restricted to the most anterior folia. Beyond the sagittal plane of the flocculus, no changes could be recognized. The remainder of the cerebellar cortex was normal.

The central white matter of the cerebellum showed only a slight increase in glial fibrils in the plane of the vermis, and a slight degree of pallor of myelin staining and gliosis in the floccular peduncles. The *dentate nucleus* was normal except in its most medial and anterodorsal portion, in which region there was moderate proliferation of microglia cells and medium-sized astrocytes but no definite nerve cell loss. There was an increased number of microglia cells and small astrocytes in the *globose, emboliform,* and *fastigial nuclei,* again without definite loss of nerve cells. In the fastigial nuclei there was also fibrous gliosis.

The *inferior* and *dorsal accessory olives* showed the same type of change in terms of nerve-cell loss and gliosis as was seen in the previous cases. The medial accessory olives were intact, however. There was loss of nerve cells and fibrous gliosis in the *superior vestibular nuclei,* but the other vestibular nuclei were normal, with the exception of a mild astrocytic hyperplasia and hypertrophy. All other nuclear masses of the brain stem were normal, as were the myelinated tracts and the cerebellar peduncles.

In the remainder of the brain, the significant changes were confined to the optic nerves, optic tracts, and lateral geniculate bodies. There was a symmetrical degeneration of the papillomacular bundles, with an appropriately localized gliosis. A minimal nerve cell loss and hyperplasia of astrocytes were noted in the lateral geniculate bodies.*

There was also a diffuse, mild astrocytic hyperplasia in the cerebral cortex. In the spinal cord there was a slight, but definite, pallor of myelin staining in the columns of Goll, with an attendant fibrillar and cellular gliosis. The mammillary bodies and adjacent parts of the hypothalamus were intact. The meninges and blood vessels were normal.

CASE 4.—*A habitual drinker, who had experienced many serious complications of alcoholism, developed a disturbance of gait in the year before his death, which resulted from hepatic coma. Pathologically, there was a degeneration, varying in degree, of all elements of the cerebellar cortex, the lesions being symmetrically distributed in the superior vermis and the most anterior portions of the anterior lobes.*

Aw, a 60-year-old man, was admitted to the hospital on May 20, 1958, because of deepening jaundice and difficulty in walking. He had been an inveterate alcoholic for at least 25 years, as was his father before him. The patient was accustomed to drink excessively for periods of five or six months, these periods being separated by much shorter periods of abstinence. He was said to have eaten poorly when he was drinking.

There had been repeated hospitalizations for chronic pancreatitis, alcoholic gastritis, and cirrhosis of the liver. Nevertheless, the patient had managed to remain employed until May, 1957. Since the beginning of 1957, he had been eating particularly poorly, and there had been a marked, although unspecified, weight loss. At this time a disorder of gait also became manifest. It had been of insidious onset and was slowly progressive. The patient was said to walk in a slow, "shuffling" manner, with small steps, and to exhibit particular difficulty in maintaining his balance when he turned or tried to seat himself in a chair. At the beginning of 1958, his speech was noticed to be thick, even when he was sober. Two weeks before admission he became completely anorectic and developed jaundice and swelling of the ankles and of the abdomen. Concomitantly, his ataxia worsened, and for these reasons he was admitted to the hospital.

On examination, he was found to be emaciated and deeply icteric and appeared critically ill. The tongue was red and smooth. The liver was hard and grossly enlarged; the abdomen was swollen with fluid, and the legs were edematous up to the thighs. The testes were atrophic. Mentally, he was vague, and his thinking was somewhat confused. Cranial nerve function was normal except for a fine horizontal nystagmus on lateral gaze to either side. The finger-to-nose test was performed

* The findings related to this aspect of the case will be the subject of a future communication.

reasonably well without intention tremor, as were other tests of muscular coordination. He was too weak to stand; hence the testing of his stance and gait was impossible. The deep reflexes were present and physiological in the arms but absent in the legs. Superficial sensation was diminished in the feet, and position sense was intact.

The laboratory findings were consistent with advanced liver disease. The spinal fluid was normal except for a faint yellow discoloration. The clinical course was one of progressive deterioration, terminating in hepatic coma and death, on June 11, 1958.

General Pathological Findings.—The skin and sclerae were markedly icteric. The liver weighed 1,820 gm., and the lobular architecture was entirely replaced by nodules, measuring from 0.2 to 1 cm. in diameter. The pancreas was hard and fibrotic; the tail contained a large cavity filled with old blood clot and adherent to the spleen and transverse colon. The spleen was firm and weighed 360 gm. Microscopically, the architecture of the liver was entirely distorted by bands of fibrous tissue. The liver cells were filled with fat, bile pigment, and "alcoholic" hyalin. There were islands of regenerated liver cells, haphazardly arranged, and an enormous proliferation of cholangioles. The splenic pulp was congested, and the Malpighian corpuscles were largely replaced by islands of fibrous tissue. The pancreatic tissue had been largely destroyed, and only fibrous and fatty tissue remained. The esophagus contained large, dilated submucosal blood vessels. Surrounding the pelvis of each kidney was an intense chronic inflammatory reaction.

Neuropathological Findings.—There was a moderate degree of convolutional atrophy in the frontal regions and some opacity of the overlying piaarachnoid. Coronal sections of the brain disclosed a moderately severe dilatation of the lateral ventricles and a gaping third ventricle. The corpus callosum was very thin, being reduced to about one-quarter its usual size. The cerebellum, after separation from the brain stem, weighed 135 gm. A moderate degree of separation of the sulci and some narrowing of the folds of the superior vermis were seen in sagittal section (Fig. 21*B*).

Microscopic Findings.—As in the preceding case, the cerebellum was involved by a symmetrical degenerative process (Figs. 6, 11). This was most severe in the *lingula, central lobule, superior culmen,* and the *most anterior folia of the anterior lobe.* The lesion of the anterior lobe was most extensive in the paravermian region and tapered off laterally; no changes were recognizable lateral to the plane of the flocculus (about 2 cm. from the midline).

In the areas of severest involvement, the molecular layer was reduced to about half its normal width but seemed to contain the usual number of superficial stellate and basket cells. The Purkinje cells were greatly reduced in number; the few remaining ones were small and pale. There was moderate proliferation of Bergmann glial cells. The granule cells were clearly reduced in number, and the entire granular layer was slightly thinner than usual (Fig. 23*A*). There was a mild astrocytic hyperplasia in this layer and a suggestion that the Golgi II cells were not present in their usual numbers. A slight thinning of the myelin sheaths in the lamellar white matter was present and accompanied by moderate astrocytic hyperplasia, and severe fibrous gliosis. Empty, delicate peri-Purkinje baskets of argentophilic nerve fibers were present in large numbers, and the deep tangential fibers were relatively preserved. Also, a large number of vertically oriented axons were seen in the molecular layers, probably representing both climbing fibers and granule-cell axons (Fig. 23*B*). Similarly, many fibers of fine caliber were present in the granule-cell layer. Small macrophages laden with fine sudanophilic droplets were scattered in small numbers throughout all the layers of the cerebellar cortex. Again, evidences of the pathological process were more pronounced in the crowns of the convolutions than in the depths.

The foregoing description needs to be modified in regard to the following details: Within a folium that was in general severely affected, segments could be found which were involved to a less severe degree. The transition between the severely and the less severely affected segments was remarkably abrupt. In the less involved segments, the granule-cell layer was intact; the molecular layer was involved very little, and Purkinje cells were lost to a variable degree.

The *inferior culmen* and the portion of the *declive bordering the primary fissure* were, on the whole, less seriously involved. In these regions the granule-cell layer was everywhere normal. The molecular layer was normal or only slightly reduced in width. In some segments the Purkinje cells were entirely lost; in others the depletion of cells was only partial. The remainder of the cerebellar cortex, including that of the flocculi, was normal.

The nerve-cell population of the deep cerebellar nuclei was normal. There was mild astrocytic hyperplasia and proliferation of rod-shaped microglia cells in the *fastigial nuclei.* The cerebellar white matter, including the fleece of the dentate nuclei and the superior and middle cerebellar peduncles, showed no significant abnormalities.

In the most medial portion of the dorsal laminae of the *inferior olives* there was a slight loss of nerve cells. The other components of the olivary complex were normal. The vestibular nuclei were

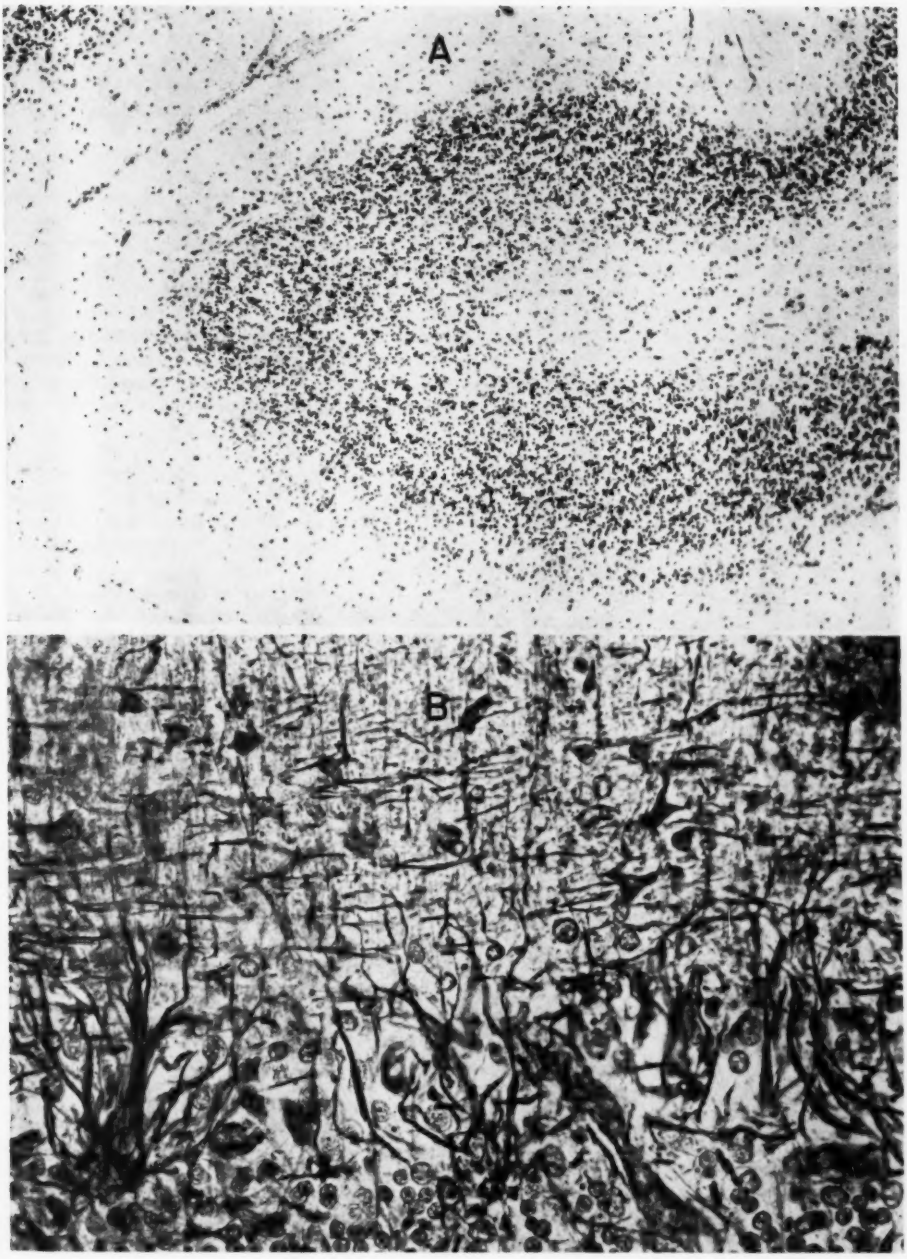


Fig. 23 (Case 4).—Central lobule. *A*, severe involvement of molecular, Purkinje cell, and granular layers. Cresyl violet stain.

B, empty, delicate peri-Purkinje basket formations and deep tangential fibers are preserved. The vertically oriented fibers in the molecular layer probably represent both climbing fibers and granule-cell axons. Cajal reduced-silver method.

normal. All other nuclear groups of the brain stem were normal, including the pontine and red nuclei and the substantia nigra. The transverse fibers of the pons were well myelinated. Aside from a slight astrocytic hyperplasia in the superior and middle cerebellar peduncles, these structures were normal, as were the restiform bodies.

A variety of other changes were seen in the remainder of the nervous system. There was a patchy loss of nerve cells throughout the cerebral cortex and an increase of pale, irregular, and lobulated astrocytic nuclei, particularly in the deeper layers. A moderate increase in astrocytic nuclei in the white matter and a fine fibrillar gliosis were observed. A sprinkling of sudanophilic droplets was present in the cytoplasm of macrophages, which were scattered in small numbers throughout the white matter, mostly in the perivascular spaces.

The corpus callosum was very thin and contained a reduced number of myelinated fibers. The internal capsules and cerebral peduncles were normal. The nerve-cell population of the basal ganglia was not reduced, but there was a proliferation of irregular, moderately large, pale astrocytic nuclei, particularly in the globus pallidus, putamen, and caudate nucleus. The hypothalamus, including the mammillary bodies, was normal.

In the spinal cord, there was a pallor of the column of Goll, most marked in the cervical region, accompanied by mild astrocytic hyperplasia and moderately severe fibrillary gliosis. In the anterior horns of the lumbar segments, many cells showed the characteristic "axonal" changes, and there was pallor of myelin staining of both the anterior and the posterior roots. Myelin sheaths in the peripheral nerves were reduced in number, and often fragmented, but the latter change was of questionable significance; there were a few macrophages containing sudanophilic droplets. Again, these were usually located in the perivascular spaces.

CASE 5.—*A middle-aged man with a background of alcoholism developed a progressive cerebellar ataxia affecting gait, legs, arms, and the speech apparatus. Pathologically, there was a symmetrical degeneration of the cerebellar cortex, practically limited to the anterior and superior portions.*

Am had suffered from a slowly progressive neurological illness for 10 years before his death, at the age of 65. At the age of 55 he first noted an unsteadiness of gait, and shortly afterward his arms became clumsy, to the extent of seriously hampering such acts as writing and eating. Concomitantly, his speech became increasingly difficult to understand. All of these symptoms became considerably worse in the last year of his life.

At the age of 25 the patient contracted tuberculosis. This was adequately treated in a sanatorium and never recurred. While in college he had first noted a mild tremor of the hands, which was not progressive and which did not seriously interfere with writing or other activities. It was considered to be a familial tremor, since his mother and brother had been similarly afflicted. There was, however, no neurological disease in the family similar to the patient's late-life cerebellar syndrome.

There was also a family history of serious alcoholism. The patient's brother had died of delirium tremens, and the father had been an excessive drinker. The patient himself had been a very serious and steady drinker in his early adult life, but his alcoholic and dietary habits in the years just preceding his later neurological illness were not clearly known. For the last eight years of his life, i.e., after his neurological disease was well advanced, he was said to have abstained from alcoholic beverages.

The patient was examined on several occasions in the two years before his death. He could stand with difficulty in the Romberg position, with variable titubation; and his head and trunk swayed even while he was seated, unless he supported himself with his arms. He was able to walk with the aid of a cane; his feet were usually placed far apart, and his steps were irregular. The legs were extremely awkward, and a gross incoordination on heel-to-shin test was noted. An incoordination of the arms, as on finger-to-nose testing, was also evident. There was a tremor of wide excursion of the outstretched arms. The speech was poorly articulated, low-pitched, and nasal. At no time was there nystagmus, and cranial nerve function was otherwise normal. The deep reflexes were always normal and the plantar responses flexor, and there was never any disturbance of sensation or of sphincteric function. The intellect remained keen throughout the illness. He died of pneumonia.

General Postmortem Findings.—The body was somewhat emaciated. Both lungs showed diffuse and severe hemorrhagic edema and focal areas of bronchopneumonia. In addition, patchy fibrosis and emphysema of the left upper lobe were found, and a healed obliterative pleuritis on the right. There was a marked diverticulosis of the sigmoid. The liver was normal except for the presence of a small hamartoma.

Neuropathological Findings.—The brain weighed 1,330 gm. The leptomeninges and the major blood vessels appeared normal. The cerebral hemispheres and brain stem were grossly normal. There was a shrinkage of the folia and widening of the sulci of the superior portion of the cerebellum.

Microscopic Findings.—Again, the major abnormality was found in the cerebellar cortex, the lesions being symmetrically distributed and most prominent in the *lingula, central lobule,* and *culmen,*

in the *portion of the declive bordering on the primary fissure*, and in the *most anterior folia of the anterior lobes* (Figs. 7, 12). As in the preceding cases, the crests of the folia were generally more affected than the depths. In these regions all the parts of the cortex were affected to a varying degree. The molecular layer was reduced to half its normal thickness and appeared more cellular than usual, the result of a moderate proliferation of small astrocytic nuclei and a slight increase of microglia. The superficial stellate and basket cells were preserved and appeared to be normal. Hardly a Purkinje cell could be found, and the few surviving ones were small and pale and had ill-defined nuclei. A moderately intense proliferation of astrocyte nuclei was present in the Purkinje-cell layer, and in places they formed a dense band, which was separated from the underlying granular layer by a clear zone. There was a reduction in the number of granule cells, and many of those remaining were pale. Golgi II cells of the granular layer were found in normal numbers, and there was a mild astrocytic proliferation.

By the use of silver impregnation methods, these severely affected regions were shown to contain an abundance of empty pericellular baskets, many of which were collapsed. Their constituent fibrils appeared rather thin and evenly impregnated. The deep tangential fibers of the molecular layer were intact for the most part, although no Purkinje axonal collaterals could be seen. Purkinje-cell dendrites had largely disappeared, and only a rare thickened axon was evident. Occasional fibers extending from the granular into the molecular layer could be seen; some of these could be identified as T-axons of the granule cells on the basis of visible branching, while others may have been climbing fibers. No mossy fibers could be identified in these heavily affected parts. The lamellar white matter showed marked proliferation of plump astrocytic nuclei and mild pallor of myelin staining.

A less severe degree of affection was found in the *pyramis*. Here there was a moderately severe patchy loss of Purkinje cells and a proliferation of Bergmann astrocytes, but the molecular and granule layers appeared normal. A number of the remaining Purkinje cells had been displaced into the granular layer. In the nodulus there were a few scattered areas of calcification, but no other significant changes. The remainder of the cerebellar cortex, including the cortex of both flocculi, disclosed no abnormalities.

The central white matter of the cerebellum was normal except for the *floccular peduncles*, which showed a mild degree of pallor with myelin stains. Also, there was a striking degree of ferruginization of thick-walled blood vessels in the vicinity of the dentate nuclei.

No definite loss of nerve cells could be seen in the dentate, globose, and emboliform nuclei, although there was a marked deposition of lipofuscin in these cells. The fleece and hilus of the dentate nuclei were normal. There were a slight astrocytic hyperplasia within the dentate nuclei and a somewhat greater proliferation of both microglia cells and astrocytes in the emboliform and globose nuclei. The fastigial nuclei were not visualized, but a definite pallor in myelin stains and gliosis were seen in the superior portion of the *medial fastigiobulbar tract*.

In the inferior olives, there was a marked nerve cell loss with gliosis in the dorsal laminae, most intense in their medial portions. The *dorsal accessory olives* were gliotic and almost completely depopulated of nerve cells. The nerve cells in the dorsal portions of the *medial accessory olives* were reduced in number (Fig. 21*C*). The fleece and hilus of the olives were normal. No reduction in the numbers of olivocerebellar fibers or in the fibers of the restiform bodies could be demonstrated. The external cuneate and lateral medullary nuclei, as well as the other reticular nuclei of the brain stem, were normal. The cochlear and the medial, spinal, and lateral vestibular nuclei were normal, but in the *superior vestibular* nuclei a moderate gliosis and loss of nerve cells were found. The pontobulbar bodies, arcuate nuclei, and nuclei of the basis pontis were entirely normal, as were the middle and superior cerebellar peduncles.

The red nuclei were normal. Occasional cells in the zona compacta of the substantia nigra were vacuolated, and widely scattered macrophages laden with melanin granules were seen, particularly around small blood vessels. However, the majority of the cells of the substantia nigra were normal.

A variety of changes were seen in other parts of the nervous system. There was pallor of staining of the myelin sheaths in the roots of the cauda equina and a mild pallor of the posterior columns of the spinal cord, particularly of the column of Goll in the cervical region. The spinocerebellar tracts were normal. There was a marked deposition of lipofuscin in the cells of the anterior horns and of Clarke's columns. Nerve cells of the thalamus also contained large amounts of lipofuscin. Ferruginization of thickened blood vessel walls was present in the globus pallidus. The lateral and third ventricles were moderately dilated. The corpus callosum and central white matter in the cerebrum were normal. Aside from the large amounts of lipofuscin in the Betz cells, the cerebral cortex was not unusual. The meninges were normal. A moderate thickening of the media of many arterioles, both meningeal and parenchymal, was noted.

CASE 6.—*A chronically malnourished and alcoholic man developed unsteadiness of gait, which worsened over a two-month period but was stationary thereafter. Examination showed cerebellar ataxia of gait and to a less extent, ataxia of the legs and arms, moderately severe polyneuropathy, and liver disease. The pathological changes in the cerebellum were confined to the vermis, being severer superiorly; and there was also evidence of Wernicke's encephalopathy.*

E, a 53-year-old gardener, was admitted to the hospital in March, 1956, for the investigation of a gait disturbance. Two months before, he had first noticed that his knees were "stiff" on arising, and that he was "shaky" while walking. He complained also of weakness in the arms and legs. These symptoms progressed steadily over the next two months, and at the end of this time he was hardly able to stand without support.

There was no family history of neurological disease. The patient stated that he had been in the habit of drinking two or three bottles of ale and "some" whisky and wine every day for many years. Also, he had been eating poorly for at least five months before admission. Six years previously he had had an episode of severe gastrointestinal bleeding, the cause of which was not determined.

The general physical examination disclosed the following significant abnormalities: The skin was thin, loose, and dry and covered with multiple telangiectases. The nails were brittle, and there was palmar erythema. The teeth and gums were in a state which indicated severe neglect. The edge of the liver was palpable 10 cm. below the costal margin. The extremities showed severe varicose veins bilaterally, with brawny pigmentation of the skin and multiple anterior tibial excoriations.

On neurological examination, there was evidence of a mild memory defect. There was no nystagmus or dysarthria. A slight degree of weakness of the legs could be demonstrated, but not of the arms. Deep tendon reflexes were present in the arms and absent in the legs. There was a mild loss of all modalities of sensation, including position sense in the fingers and toes. A slight intention tremor could be brought out by finger-to-nose, heel-to-shin, and toe-to-finger testing. The patient stood on a rather wide base and swayed excessively in the Romberg position. He was able to walk without support but in a slow, unsteady manner.

The important laboratory findings were sulfobromophthalein (Bromsulphthalein) retention, 20%; cephalin flocculation, 4+; reversal of the serum albumin-globulin ratio; prothrombin time 68% of normal. There was also suggestive roentgenological evidence of esophageal varices.

In August, 1956, the patient was discovered to have a squamous-cell carcinoma of the larynx, with metastases to the cervical lymph nodes. X-ray therapy and implantation of radium in the neck produced a temporary regression of the tumor masses, but eventually his airway was compromised by continuing tumor growth, and he died of terminal pneumonia in July, 1957. His neurological state did not change from the time of his first admission, in March, 1956.

General Postmortem Findings.—The patient was very thin. The larynx contained a large, locally invasive squamous-cell carcinoma. The entire right lung was consolidated and showed the characteristic picture of lobar pneumonia. The liver weighed 1,720 gm. and was firm and nodular; histologically there was an increase of periportal fibrous tissue and proliferation of the bile ducts. The spleen weighed 300 gm. and was congested. There was moderate atrophy of the germinal epithelium of the testes.

Neuropathological Findings.—The brain weighed 1,300 gm., and there was some thickening and opacity of the leptomeninges. The large arteries were normal. The frontal convolutions were slightly atrophic. Coronal sections through the cerebral hemispheres disclosed that the mammillary bodies were smaller than usual; there was a small cavity in one and a grayish discoloration of the other. The third ventricle was wider than normal.

The cerebellum, after removal from the brain stem, weighed 130 gm. On sagittal section there appeared to be a widening of the sulci between the folia of the superior vermis.

Microscopic Examination.—The significant changes in the cerebellar cortex were entirely confined to the vermis (Fig. 8). There was a severe loss of Purkinje cells in the *lingula, central lobule,* and *superior portion of the culmen,* although even in the most severely affected folia some shrunken pyknotic Purkinje cells could be seen. The molecular layer in these regions was narrowed to about half the normal width, but the superficial stellate and basket cells were preserved. There was a definite increase in number and thickness of the Bergmann glia fibrils but no frank hyperplasia of the cell bodies themselves. A moderate loss of granule cells was also present, but the Golgi II cells of this layer were normal (Fig. 24*A*). In most places the cell loss and gliosis were severer at the crests than in the depths of the folia. The pericellular baskets were generally preserved and did not appear abnormally thickened. There was mild thinning of the deep tangential fibers of the molecular layer. The T-axons of the granule cells and climbing fibers were still seen in the most severely affected regions, but mossy fibers could not be identified with certainty. The Purkinje-cell dendrites, axons, and recurrent collaterals of the axons had all disappeared. A mild reduction in the num-

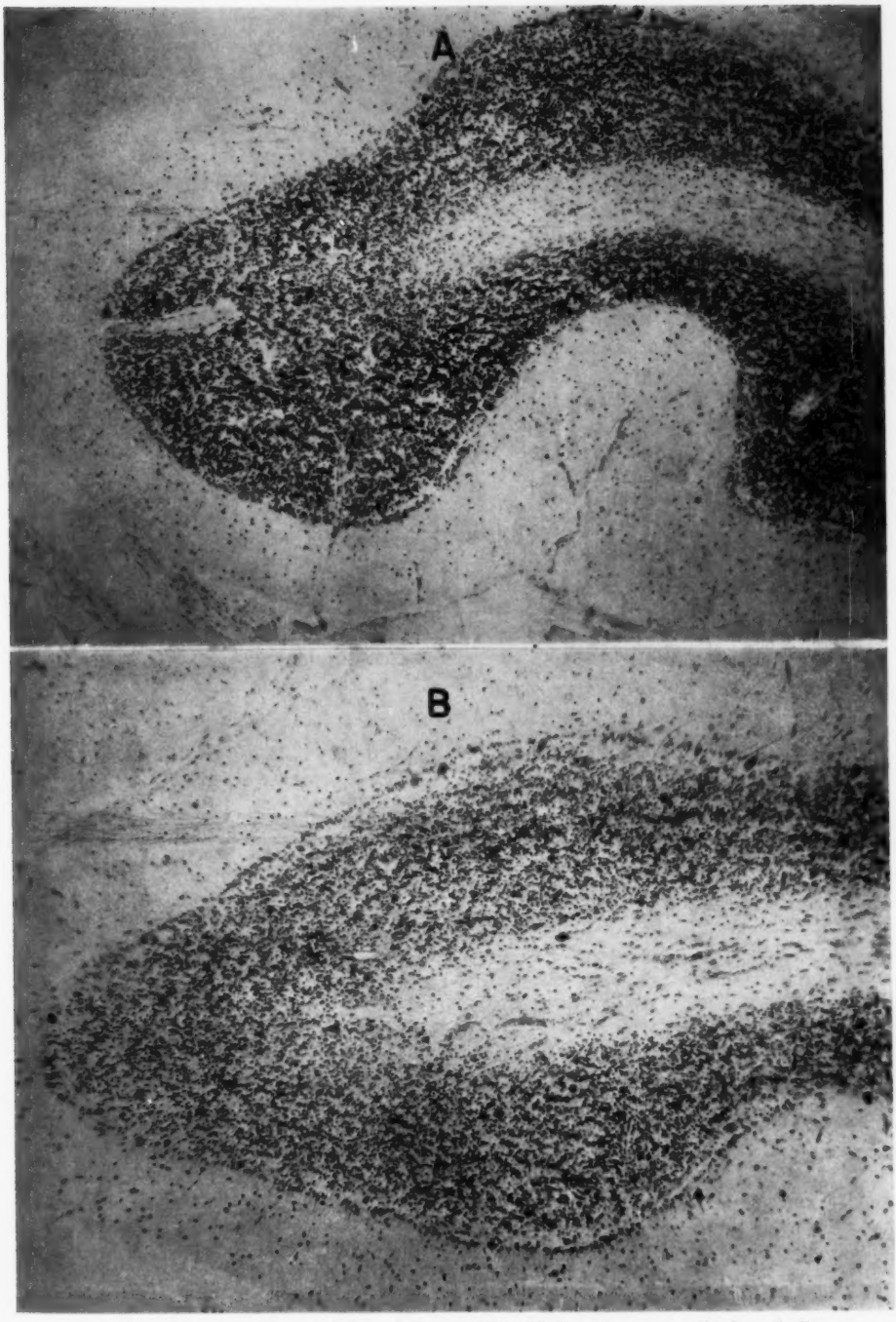


Fig. 24.—Culmen of Case 6 (*A*) and Case 8 (*B*). Moderately severe affection of all portions of the cortex, somewhat more pronounced in *A*. Cresyl violet stain.

ber of axis cylinders in the cores of these lamellae was observed; a few abnormally swollen axis cylinders and some fragmented bulbous forms could be seen here. A mild pallor of myelin staining was also observed in the lamellar white matter, as well as an increased number of astrocyte nuclei.

The *posterior part of the culmen* and the *superior portion of the declive*, i.e., those parts adjacent to the primary fissure, and the *nodulus* also showed a definite reduction in the number of Purkinje cells, but this change was not nearly as severe as in the superior parts of the vermis. In these less affected regions the molecular layer was only slightly reduced in width, and there was no discernible loss of granule cells. The remainder of the vermis was normal, as were the entire cerebellar hemispheres, including the flocculi. The central white matter of the cerebellum, the floccular peduncles, and the fleece of the dentate nuclei appeared to be normal. Within the dentate nuclei themselves there was a slight patchy loss of nerve cells, with a mild degree of astrocytic proliferation. The emboliform and globose were normal. There was definite proliferation of microglial and astrocytic nuclei in the *fastigial nuclei*, and perhaps a loss of nerve cells as well.

A severe nerve loss and gliosis were observed in the medial portions of the dorsal laminae of both *inferior olives*, as well as throughout the *dorsal accessory olives*, and in the dorsal portions of both *medial accessory* olives. Both the fleece and the hilus of the inferior olives showed a reduction in the number of myelinated fibers. There was also pallor in the central portions of the *restiform bodies*, but no apparent decrease in number of the internal arcuate fibers. The *dorsal motor nuclei of the vagus* showed a moderate loss of nerve cells and a proliferation of microglia cells and astrocytes. In the *nucleus gigantocellularis reticularis* of both sides there were ballooned cells with eccentric nuclei, glassy cytoplasm, and chromatolysis, with margination of the remaining Nissl material. The other reticular nuclei, the arcuate nuclei, the nuclei of the posterior columns, and the pontobulbar bodies were normal. A patchy nerve cell loss and gliosis were noted in the *superior vestibular nuclei*. The spinal, medial, and lateral vestibular nuclei were probably normal.

The nuclei of both the tegmentum and the basis of the pons were normal, as were the transverse pontocerebellar fibers and the middle cerebellar peduncles. Also, the superior cerebellar peduncles were well myelinated, but they contained a scattering of plump astrocytes, which were particularly prominent at the point of their decussation in the lower midbrain. The nerve cells of the red nuclei were normal, although a mild proliferation of astrocytes could be discerned within these nuclei. A small amount of melanin was seen within macrophages in the substantia nigra. There was a diminution in the number of nerve cells with gliosis in the dorsomedial portions of both oculomotor nuclei, and a proliferation of astrocytes in the median raphe and beneath the floor of the aqueduct.

The central portions of the mammillary bodies were almost entirely depopulated of nerve cells and were the site of a moderately severe fibrous gliosis. The blood vessels here were not unusual in appearance. A similar but patchy loss of nerve cells with gliosis was seen in the medial nuclei of the thalamus and in the nuclei bordering the third ventricle. The rest of the basal ganglia were normal, as were the corpus callosum and centrum ovale. There was a mild patchy loss of nerve cells in the hippocampus, but the cerebral cortex was otherwise unremarkable.

Comment.—Clinically, the cerebellar disease was less severe than in most of our patients. Similarly, the pathological changes were more restricted and generally less intense than those seen in the preceding five cases. In this case the polyneuropathy must have contributed to the ataxia to a greater extent than usual. The carcinoma of the larynx was probably not related to the cerebellar changes, in view of their restricted topography. These points will be elaborated in the discussion.

CASE 7.—*An inveterate alcoholic man developed Korsakoff's psychosis and ataxia of gait. Postmortem examination, three years later, revealed changes characteristic of the Wernicke-Korsakoff syndrome, and also a severe loss of Purkinje cells in the superior vermis.*

Au had been a heavy drinker since the age of 30 and had been hospitalized on numerous occasions for bouts of hematemesis and melena, which culminated in a partial gastrectomy, at the age of 55. At this time no abnormal neurological or mental signs were noted. The patient was not seen until two years later, when he was readmitted to the hospital in a state of confusion. He was thin and appeared poorly nourished. He was disoriented and was said to confabulate at the slightest provocation. His memory, particularly for recent events, was extremely impaired, as was his ability to learn and to retain newly presented facts. The other striking feature of the neurological examination was the ataxia of gait. There was no nystagmus and no reflex or sensory loss. The plantar reflexes were flexor. Speech was considered normal.

Because of the amnestic psychosis, the patient was transferred to a state mental hospital, where

he remained, essentially unchanged, until his death, three years later, from acute intestinal obstruction.

General Pathological Examination.—Autopsy disclosed volvulus with infarction of the small bowel. There was also generalized and coronary atherosclerosis, with occlusion of the anterior descending branch of the left coronary artery and acute dilatation of the left ventricle. There was no cirrhosis of the liver.

Neuropathological Examination.—Inspection showed a yellowish-brown discoloration of the mammillary bodies and of the region ventral to the aqueduct at the level of the inferior colliculus. There were no other gross abnormalities.

Microscopic Examination.—There was a severe degree of nerve cell loss and gliosis in the central portions of the mammillary bodies and the medial thalamic nuclei, characteristic of an old Wernicke encephalopathy.

In addition, there was a lesion of the cerebellum, limited to the *central lobule* and to the *adjacent folia of the lingula and culmen* (Fig. 8). In these regions there was a severe loss of Purkinje cells, accompanied by a mild proliferation of the Bergmann astrocytes. There were a few small collections of microglia cells in the Purkinje-cell layer, suggesting "glial bushes." The molecular and granular layers and the underlying white matter were normal. The remainder of the cerebellar cortex, the cerebellar white matter, and all the deep cerebellar, olivary, and reticular nuclei showed no abnormalities. The spinal and medial vestibular nuclei were normal; the superior and lateral nuclei could not be identified; the cerebellar peduncles were intact. There was a mild patchy loss of nerve cells in the cerebral cortex.

Comment.—Unfortunately, the exact time of onset and mode of evolution of both the memory disturbance and the ataxia could not be determined. Also, the clinical extent of the cerebellar ataxia was incompletely determined. The salient pathological feature was the restriction of the cerebellar changes to discrete portions of the superior vermis.

In the cases which have just been described, there was clear evidence that a cerebellar syndrome had been present during life. In the four cases which follow such evidence was wanting. This is not to say that these patients necessarily lacked the clinical signs of cerebellar disease—they were not personally examined during life, and it is possible that such signs may have been overlooked, particularly in Cases 9 and 10, in which the patients were critically ill and no history was available. For this reason the first 7 cases have been set apart from the 4 which follow, although the pathological changes in the cerebellum were essentially the same in all 11 cases. In the latter group, of four cases, the cerebellar disease was an incidental finding, discovered in the course of our neuropathological studies of alcoholism in general.

CASE 8.—A 60-year-old woman was admitted to the hospital on July 11, 1955, because of severe weakness and confusion of recent onset. She had been drinking to great excess and eating very poorly for many years, as attested by several hospitalizations for acute and chronic alcoholism, malnutrition and dehydration, and alcoholic gastritis. In 1951 she developed severe nutritional megaloblastic anemia, but even this episode failed to alter her drinking and dietary habits. One week before her final admission to the hospital, she became confused and unable to rise from her bed.

On examination, on July 11, 1955, the patient appeared very pale, dehydrated, and obviously undernourished. The major neurological abnormalities were those of acute Wernicke's encephalopathy, i.e., a quiet confusional state, bilateral abducens paralysis, vertical nystagmus, and a disorder of gait. There was also evidence of a mild polyneuropathy affecting the legs. Treatment with thiamine produced a dramatic improvement in the ocular signs, but the gait recovered slowly, and only incompletely by Aug. 16. On that date the patient was transferred to a state mental hospital because of the presence of a severe amnestic psychosis, which had become increasingly evident as she recovered from the ophthalmoplegia and acute confusional symptoms. Nine days after admission to the mental hospital she suddenly lapsed into coma and died.

Postmortem Examination.—Autopsy was limited to the head: The brain weighed 1,000 gm. in the unfixed state. A slight convolutional atrophy was present. There was only a minimal degree of atherosclerosis. The mammillary bodies were discolored and gave the appearance of being the seat of old hemorrhage. The walls of the third ventricle above the mammillary bodies were gray, and the ventricle was wider than normal. The cerebellum weighed 120 gm. after fixation. The inferior colliculi looked gray and mottled.

Microscopic Examination.—The alterations in the cerebellar cortex were confined to the superior vermis (Fig. 8). The most severely affected portions were the *lingula* and some folia of the *central lobule*. Here, there was a marked outfall of Purkinje cells and a slight proliferation of

the Bergmann glia. The molecular layer was narrowed, but the small nerve cells of this layer were present in normal numbers. Deep in the molecular layer occasional small clusters of pleomorphic microglia cells were seen. There was a recognizable loss of granule cells, although the Golgi II cells in this layer appeared normal.

The remainder of the *central lobule*, the *culmen*, and *the portion of the declive bordering the primary fissure* were distinctly involved, though to a less degree. In these regions there was a moderate loss of Purkinje cells, but the molecular and granular layers were unaffected and there was no clear proliferation of the Bergmann glia (Fig. 24*B*). The remainder of the vermis and the cerebellar hemispheres, including the flocculi, was entirely normal. The white matter of the cerebellum was intact, as were the deep cerebellar nuclei, except for a mild degree of hyperplasia of small astrocytes.

In the *inferior olives* there was a severe loss of nerve cells with a marked gliosis, affecting the medial two-thirds of the dorsal laminae. A similar change was present throughout the *dorsal* and *medial accessory olives*. All other nuclear groups in the brain stem, including the vestibular complex and the cerebellar peduncles, had a normal appearance. Other alterations of significance were found in the mammillary bodies and in the structures bordering the third ventricle; these changes were considered characteristic of Wernicke's disease. Also, there was a mild patchy neuronal loss and astrocytic proliferation in the cerebral cortex. The meninges were slightly thickened and the blood vessels showed no important abnormalities.

Comment.—Cases 7 and 8 may be commented upon together, since their clinical and pathological features were so similar. Both patients developed Wernicke's disease on a background of prolonged alcoholism and malnutrition, and in both a residual amnestic psychosis and a persistent disturbance of gait were prominent clinical features, although in Case 8 the cerebellar nature of the ataxia was never clearly established during life. The pathological findings were also similar in the two patients, in regard to the lesions both of Wernicke's disease and of cerebellar degeneration. These cases raise the interesting problem of the relationship between these two diseases, a matter which will be commented upon further under "Comment."

CASE 9.—A 46-year-old man was admitted to the hospital on Feb. 3, 1957, because of jaundice, ascites, and peripheral edema, of two weeks' duration. The patient had been an unremitting drinker for many years and for the previous four years had been unemployed because of his excessive alcoholic intake. His past history was replete with the most serious complications of alcoholism. He had had delirium tremens at least once, and attacks of tremulousness and vomiting had been commonplace. Also, there had been two episodes of jaundice and lethargy, each lasting two or three months, accompanied by gastrointestinal bleeding.

The patient was cachectic and slightly icteric, with great swelling of the abdomen, legs, and genitalia. Despite the massive ascites, he weighed 151 lb., in contrast to his optimum weight of 175 lb. Muscle wasting was particularly prominent in the extremities. Deep reflexes were brisk and equal in the arms but barely obtainable at the knees and absent at the ankles. The plantar responses were flexor. Laboratory examinations disclosed normocytic anemia and a number of biochemical abnormalities characteristic of severe liver disease. During his hospitalization he suffered a recurrence of severe gastrointestinal bleeding, subsequent to which he lapsed into a protracted coma, with death on March 25, 1957.

General Pathological Findings.—The immediate cause of death was acute bronchopneumonia. The coronary arteries were markedly atherosclerotic, and an old septal infarct was demonstrated. There were small esophageal varices, a healed duodenal ulcer, and 800 ml. of ascitic fluid. Several calculi occluded the common bile duct, the biliary and hepatic ducts proximally being dilated and ruptured, producing secondary bile peritonitis. The liver showed biliary cirrhosis. There was a moderate degree of splenomegaly and testicular atrophy, and in the kidneys there was evidence of bile nephrosis.

Microscopic Examination.—The most severely affected portions of the cerebellar cortex were the *lingula*, the *central lobule*, the *superior culmen*, those *folia of the inferior culmen and of the declive which bordered on the primary fissure*, and *the most anterior and superior folia of the anterior lobes* (Figs. 7, 12). The involvement of the anterior lobes did not extend beyond the sagittal plane of the flocculi. The pattern of involvement was thus very much the same as in the previous cases, particularly Cases 1-5. However, the severity of involvement was somewhat less; the granular layer was everywhere normal, and the molecular layer was reduced only slightly in width. The small nerve cells of the molecular layer were normal, but there was an increase in small astrocytes; and just above the Purkinje cell layer a few clusters of microglia cells were in evidence. The Purkinje cells were markedly reduced in number; most of the ones which remained were small and pyknotic

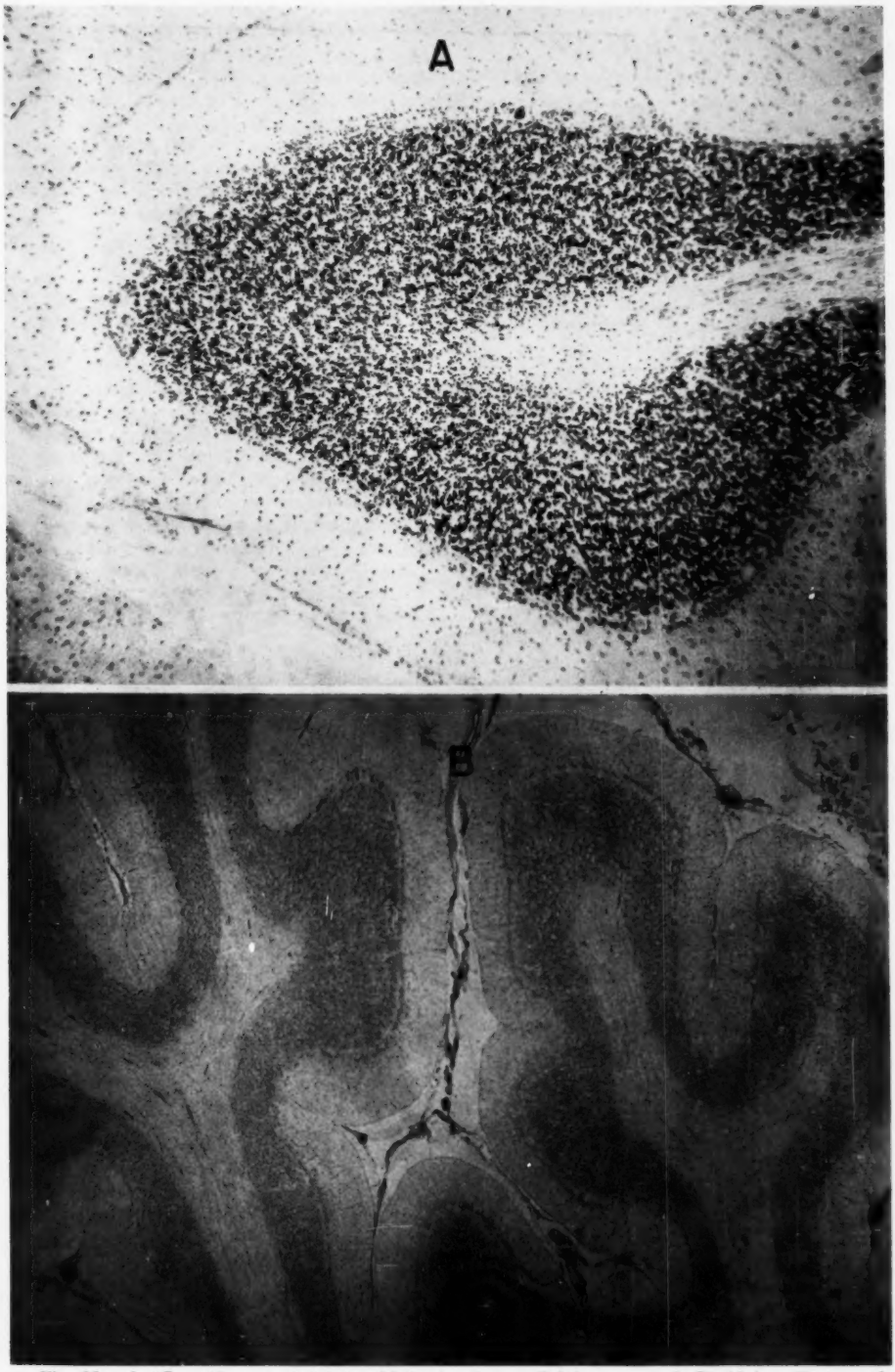


Fig. 25.—*A* (Case 9), central lobule. Molecular layer slightly narrowed, Purkinje cells severely reduced in number. The granular layer is normal. Cresyl violet stain.

B (Case 10), low-power view of central lobule (on right) and culmen (on left). The former is considerably more affected. Cresyl violet stain.

(Fig. 25*A*). The lamellar white matter was not affected. Again, the cerebellar cortex was involved in a patchy manner, segments showing only a moderate loss of Purkinje cells, lying adjacent to ones more seriously involved. The cortex of the remainder of the vermis and cerebellar hemispheres was intact.

The central white matter of the cerebellum, including the fleece of the dentate nuclei, was normally myelinated. There was a mild patchy loss of nerve cells in the *dentate nuclei* and a moderate proliferation of large, pale, irregular astrocytic nuclei. This type of astrocytic change was present in all the other deep cerebellar nuclei, although their nerve-cell population appeared normal. A moderately severe fibrillar gliosis, as determined with the Holzer stain, occupied the dorsal lamina of the dentate nuclei and was diffuse throughout the other deep nuclei. There was, in addition, a mild microglial proliferation in the *emboliform*, *globose*, and *fastigial nuclei*.

In the most medial folds of the dorsal laminae of the *inferior olives*, nerve cells were somewhat reduced in number. The remainder of the olivary complex, the arcuate and reticular nuclei, and the nuclei of the posterior columns were normal. In the medial and spinal vestibular nuclei and the red nuclei there was no loss of nerve cells, although here, too, there was a proliferation of large, pale protoplasmic astrocytes. The superior and lateral vestibular nuclei were not seen. In the substantia nigra the amount of pigment in many of the nerve cells was reduced, and scattered macrophages were seen to contain melanin granules. All the cerebellar peduncles were normal.

Throughout the cerebral cortex there was a mild patchy loss of nerve cells and a moderate hyperplasia of pale, irregular astrocytes. A similar astrocytic hyperplasia was present in the lenticular nuclei.

CASE 10.—A 58-year-old woman was admitted to the hospital because of hematemesis. Addiction to alcohol had been an ineradicable problem for 30 years. She had had numerous attacks of tremulousness, and delirium tremens had occurred on at least one occasion, 19 years before.

The patient was lethargic and slightly icteric. The tongue was dry and red, and the liver was palpable 5 cm. below the costal margin. She was found to be anemic, and her stools contained a large amount of blood. There was no ocular abnormality and no evidence of polyneuropathy.

On the day after admission the patient became restless and confused and shortly thereafter she developed full-blown delirium tremens. This was complicated on the following day by peripheral circulatory collapse, leading rapidly to death.

General Pathological Examination.—The findings of importance were pulmonary edema and congestion, atrophic gastritis, and fatty infiltration and cirrhosis of the liver. Aside from the slight frontal convolutional atrophy, there were no significant gross *neuropathological findings*.

Microscopic Examination.—There was a marked loss of Purkinje cells in the *lingula*, *central lobule*, and the most *superior folia of the culmen* (Fig. 9). In these regions the molecular layer was slightly narrowed and contained an increased number of small astrocytic nuclei. The superficial stellate and basket cells were normal. The Bergmann glial cells were moderately proliferated. The granule cells were pale but were present in normal numbers, as were the Golgi II cells. In the other folia of the culmen, particularly those bordering on the primary fissure, there was only a moderate loss of Purkinje cells and the other cortical elements appeared normal (Fig. 25*B*). The remainder of the cerebellar cortex in the vermis and throughout the hemispheres was normal. The cerebellar white matter was intact. In the vicinity of the *dentate nuclei* there was ferruginization in the walls of small arteries and arterioles. The nerve cells of the deep cerebellar nuclei were normal in number, although they were stuffed with lipofuscin granules. Throughout the dentate nuclei there was a proliferation of microglia cells and of astrocytes, the majority of which had small, irregular nuclei. A mild loss of nerve cells in the medial portion of the dorsal laminae of the *inferior olives* had occurred, and a similar loss of nerve cells with gliosis was noted in the *dorsal accessory olives*. The medial and spinal vestibular nuclei were normal. The remainder of the vestibular complex was not visualized. All the other nuclear groups of the brain stem were normal, as were the cerebellar peduncles. The cerebral cortex showed a mild astrocytic hyperplasia. The remainder of the brain was normal.

CASE 11.—This chronic alcoholic man had been hospitalized on numerous occasions for alcoholic gastritis, epilepsy, delirium tremens, chronic pulmonary infection, and a variety of traumatic incidents. His final admission, at the age of 51, was in April, 1953, in a state of postepileptic coma. As he improved, a profound and bizarre dementia became evident, characterized by disorientation, marked lack of spontaneity, and a general disturbance of cognitive function. At this time the patient was subjected to repeated neurological examinations, which consistently demonstrated loss of strength and muscle bulk in the legs, accompanied by loss of superficial sensation and of the ankle jerks. It was clearly stated, however, that the gait was not ataxic; nor were there other signs of cerebellar disease, and nystagmus was absent. Spinal fluid examinations were normal. The patient was transferred to a state mental hospital, where his dementia changed little and where he died, two years later, in status epilepticus.

General Pathological Examination.—The findings were chronic adhesive pericarditis, acute passive congestion of the lungs, bronchiectasis, fatty degeneration of the liver, and passive congestion of the spleen.

Neuropathological Findings.—The brain weighed 1,350 gm. The leptomeninges were opaque, particularly over the right postcentral convolution; and there was a brownish discolored defect in the underlying cortex. A similar old destructive lesion, involving both the cortex and the white matter, was present in the left parieto-occipital region, and another, in the right superior temporal gyrus. These lesions had the distribution and appearance of old cerebral contusions (*plaques jaunes*). The lateral ventricles were dilated to about twice their normal size. No other gross abnormalities were seen. The cerebellum, after removal from the brain stem, weighed 170 gm.

Microscopic Findings.—The scattered lesions of the cerebral cortex and underlying white matter consisted of glial scars, and a moderate number of macrophages containing blood pigment were still present. There was also patchy diffuse loss of nerve cells in the cerebral cortex. Apart from these lesions, the only important findings were in the cerebellum (Fig. 9). Here a severe loss of Purkinje cells was noted, with narrowing of the molecular layer and thinning of the granular layer in the *lingula* and *the superior half of the central lobule*. The Bergmann glial cells had proliferated. The small nerve cells of the molecular layer and the Golgi II cells of the granular layer appeared intact. In the *remainder of the central lobule* there was a distinct, but much less intense, loss of Purkinje cells; other cortical elements were normal. The other portions of the cerebellar cortex were intact. The white matter and central nuclei of the cerebellum were normal, as were all the nuclear groups of the brain stem and the cerebellar peduncles. There was no evidence of Wernicke's disease.

Comment.—In this case, we were quite certain that no cerebellar symptoms or signs had existed during life. Of interest in this connection was the remarkably restricted distribution of the lesions in the most superior folia of the vermis. The cerebellar lesions could not be considered secondary to the cerebral disease. The convulsive state was surely related to the cortical lesions. The dementia probably had as its basis the scattered cerebral lesions and the slight brain atrophy.

A Quantitative Estimation of the Changes in the Cerebellar Cortex

An attempt was made to quantitate more precisely the changes in the cerebellar cortex. Although, as has been stressed, all elements of the cortex were involved in this disease process, it was decided that the Purkinje cells, because of their size, could most easily be assessed in terms of numbers. We therefore undertook to count the Purkinje cells in a series of representative sections taken from the cases of cerebellar degeneration and from suitable control subjects.

All counts were made in Nissl-stained, celloidin-embodied sections 10μ in thickness and prepared from formalin-fixed tissue. The sections were always cut in the sagittal plane through the vermis. It was obviously impossible to have all sections in an identical plane; however, this feature did not introduce a significant error, since it has been our observation that the Purkinje-cell population in the normal brain is quantitatively homogeneous at all levels of the vermis. Only those Purkinje cells with visible nuclear structures were counted. It soon became apparent that counting the total number of Purkinje cells in any given portion of the vermis was only of limited value, because of the variation in size of the folia and lobules from area to area and from one case to another. An attempt was made, therefore, to estimate the relative population of Purkinje cells, i.e., the number of cells per unit length of cerebellar cortex. It was felt that such a figure might allow more meaningful comparisons to be made between cases or with controls. The method of determining the length of cerebellar cortex will be outlined in detail in a future communication.[7] In essence, it consists of measuring the length of any given segment, by the use of a planimeter, on an enlarged projected image of the actual section. Once the length and absolute number of cells were known, the determination of the average number of cells per millimeter was a matter of simple mathematics.

TABLE 4.—*Purkinje-Cell Counts in Alcoholic Patients*

Group I: Alcoholic Patients with Cerebellar Degeneration

	Case 2			Case 3			Case 4			Case 6		
	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.
Lingula	0	20.0	0	10	10.5	1.0	7	16.5	0.4	58	19.5	3.0
Central lobule	11	25.0	0.4	63	59	1.1	14	55.0	0.3	224	67.0	3.3
Culmen	90	180.5	0.5	231	191	1.2	114	185.0	0.6	456	215.5	2.2
Declive and folium	220	87.0	2.5	376	101	3.7	312	131.5	2.4	465	132.0	3.5
Tuber	116	84.5	1.4	198	78	2.5	100	55.0	1.8	163	45.0	3.6
Pyramis	145	64.5	2.3	521	122.5	4.3	240	110.5	2.2	333	116.5	2.9
Uvula	58	29.0	2.0	321	116.5	2.8	492	119.0	4.1	543	129.0	4.2
Nodulus	59	14.0	4.2	414	29.5	1.4	196	37.0	5.5	235	47.5	5.0

Group II: Alcoholic Patients with No Neurological Disease

	Case 1 (Age 39)			Case 2 (Age 61)		
	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.
Lingula	61	10.0	6.1	60	10.0	6.0
Central lobule	330	58.5	5.7	328	59.0	5.6
Culmen	1,445	275.0	5.3	1,020	230.5	4.5
Declive and folium	675	154.0	4.4	713	135.5	5.3
Tuber	250	70.0	3.6	328	76.0	4.3
Pyramis	533	150.0	3.6	457	109.0	4.2
Uvula	497	131.0	3.8	387	90.5	4.3
Nodulus	257	56.0	4.2	328	45.0	7.3

Group III: Normal Controls (Nonalcoholic Patients with No Neurological Disease)

	1. Age 45			2. Age 53			3. Age 57			4. Age 61		
	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Cout	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.
Lingula	108	22	4.9	95	18.5	5.1	38	5.5	6.9	104	29.5	3.5
Central lobule	378	66	5.7	370	61.5	6.0	300	68.5	4.4	381	45.0	8.5
Culmen	920	191	4.8	1,012	214.5	4.7	918	235.0	3.9	870	216.5	4.1
Declive and folium	694	140	5.0	805	116.5	6.7	603	152.5	4.0	547	133.0	4.2
Tuber				313	62	5.1	144	36.0	4.0	137	41.5	3.3
Pyramis	406	88.5	5.0	407	93.5	4.4	360	108.0	3.3	410	111.5	3.6
Uvula	412	59	7.0	589	124.5	4.7	334	85.0	4.5	405	77.0	5.3
Nodulus	404	84	4.5	203	44	4.6	161	26.5	6.1	375	79.5	4.8

Of our 11 pathologically verified cases, only 2 could not be assessed in this way. In Case 1, the sections were taken in the horizontal, rather than the sagittal, plane; Case 5 was excluded because a single section which included the entire vermis was not available. The control material was taken from 10 patients, all of whom were free of neurological disease. Two of these patients were alcoholics and eight were nonalcoholic, and they ranged in age from 45 to 90 years.

The results of these determinations are presented in Table 4. There was on the whole a striking difference, particularly in the relative Purkinje-cell population, between the alcoholic patients with cerebellar disease and the control material. In most of the normal cerebellums, whether of alcoholic or of nonalcoholic patients, the Purkinje-cell population ranged from 3.5 to 6.5 or 7.0 cells per millimeter, whereas in the affected regions of the diseased cerebellums figures of less than 2 cells per

Case 7			Case 8			Case 9			Case 10			Case 11		
Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.
35	12.5	2.8	24	7.5	3.2	12	6	0.2	1	3.0	0.3	13	4	3.3
222	88	2.5	195	65.0	3.0	70	45	1.4	50	56.0	0.9	100	35.5	2.8
725	232	3.1	553	233.0	2.4	381	200.5	1.9	533	183.5	2.9	856	217.5	3.9
601	142	4.2	530	180.5	2.9	301	140.5	2.1	830	112.5	7.4	680	139.5	4.9
332	70	4.7	189	69.0	2.7	155	54.5	2.8	285	101.5	2.8	177	54.5	3.2
351	92	3.8	266	115.0	2.3	231	102.5	2.3	484	114.0	4.3	496	94.5	5.3
315	74	4.3	288	107.0	2.7	315	150.5	2.1	277	55.0	5.0	670	64 0	10.5
242	43	4.6	270	55.0	4.9	190	37.5	5.1	128	21.5	6.0	427	48.5	8.8

5. Age 71			6. Age 71			7. Age 82			8. Age 90		
Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.	Total Count	Length of Cortex, Mm.	Purkinje Cells/ Mm.
33	13.5	2.5	22	5.5	4.0	40	6.5	6.2	10	3.0	3.3
200	53.5	3.7	220	70.5	3.1	219	45.0	4.9	182	52.0	3.5
603	176.5	3.4	774	234.5	3.3	903	236.5	4.0	614	225.5	2.7
372	102.5	3.6	439	132.0	3.9	541	120.5	4.5	344	120.0	2.9
252	72	3.5	78	58.5	1.3	135	47.5	2.9	293	85.5	3.4
263	82	3.2	395	141.0	2.8	380	91.5	4.2	249	95.0	2.6
328	94	3.5	423	120.0	3.5	405	90.0	4.5	360	121.5	3.0
105	25	4.2	132	47.0	2.8	232	40.5	5.7	122	35.5	3.4

millimeter were common. One must be cautious in the interpretation of these figures, for several reasons. First, the relative Purkinje-cell count is an average figure for any given anatomic segment, and therefore does not necessarily indicate the severity of affection, because of the tendency of the cortical involvement to be patchy and unequal in degree in any given region. Second, the figure of relative cell population could be misleading in some instances, since the factor of shrinkage would not be taken into account in such a calculation. Obviously, if the affected region had become very shrunken and the cortical length significantly less than normal, the relative population density of the remaining Purkinje cells would not reflect the actual cell loss. In such instances, the absolute cell counts and the actual length of cortex must also be taken into account. Despite these reservations, the quantitative data support, in a general way, the findings recorded in the section on pathological ob-

servations. In some instances, e.g., the tuber of Case 2, the Purkinje-cell counts suggested the presence of subtle changes which had otherwise not been apparent to us.

It is of interest that there was a reduction in the Purkinje-cell counts in three of the four control subjects past the age of 70; these patients had no signs of cerebellar or other neurological disease during life. In these cases, the absolute reduction of Purkinje cells was more pronounced than the relative reduction, indicating the presence of generalized shrinkage of the organ. However, even in these cases the reduction in number could only be considered mild in comparison with the severe changes encountered in our pathological material. In general, these data do not support the contention of Ellis [8] that in senility the more anterior and superior portions of the cerebellar cortex suffer a more significant loss of Purkinje cells than the more posterior and inferior portions, although, admittedly, his figures were concerned with the hemispheres rather than the vermis.

Comment

A. Clinical Features

Our clinical observations, based on the examination of 50 patients, have been described in detail and need only be summarized here. The clinical features were remarkably stereotyped. In every patient there was an abnormality of stance and gait, characteristically cerebellar in nature, and in almost every one this represented the most prominent disability. An equally prominent feature was the incoordination of the individual movements of the legs; in contrast, the arms were involved only to a slight extent. More than half the patients had no nystagmus or disturbance of speech function; and, even when present, these abnormalities were almost invariably mild in degree. Instability of the trunk was a common finding, but an independent tremor of the head was much less frequent. Hypotonia, ocular dysmetria, and a postural, nonintention type of tremor were relatively unusual findings.

Certain features of this syndrome require special comment. Certainly the most impressive of these was the stereotypy of the clinical picture, in regard not only to the pattern of involvement but also to the severity. Of the 50 patients, only 2 did not conform to the usual clinical picture. One of these was Patient Ag (Table 1, Group IIb), in whom the arms were affected more severely than the legs. Another patient, Ao (Table 1, Group IIIa), was distinctive in regard to the severity of the symptoms and signs. In neither of these patients has a pathological examination been possible, so that one can only speculate on the reasons for these unusual clinical manifestations. It is possible, considering the ubiquity of alcoholism in our community, that these two patients were afflicted with a disease process which differs pathologically from that of the group at large. On the other hand, it is possible, at least in Patient Ao, that the disease process was basically the same, differing only in extent or severity.

Other features worthy of comment concern certain aspects of the gait disorder. In some patients, following long periods of stability of the disease process, a change occurred in the character of the gait. The nature of this change has already been described. It is worth emphasizing that such a patient is capable of walking long distances and that one cannot judge the full extent of the disorder simply by watching him walk. Only when the patient was required to make a rapid postural adjustment or to walk heel-to-toe, did he betray the seriousness of his disability. The reason for the improvement in walking is not entirely clear. Possibly with prolonged practice the patient simply learns to walk better. It is likely that a number of other events play a role in the improvement—abstention from alcohol, improvement in general health, and recovery from a mild coexistent polyneuropathy.

We have also alluded to the curious tightening of the leg and trunk muscles which occurred in some patients when they

stood or walked without support, and which lessened or disappeared entirely when they were supine or able to support their weight artificially. Such an abnormality of muscle tone cannot properly be designated as "rigidity." It is possible that this phenomenon is analogous to the positive supporting reactions which Rademaker observed in cerebellectomized cats and dogs.[9] However, so little information is available concerning these reactions in the human that one hesitates to accept this interpretation. Another clinical feature which does not have a ready explanation concerns the remarkable stabilizing effect which a light contactual stimulus has upon the patient's unsteadiness. No weight bearing is involved in this maneuver, the barest touch of the hand with a neighboring object sometimes sufficing to steady the patient perceptibly.

A few supplementary remarks should also be made regarding the natural history of the illness (Fig. 1). In the majority of the patients two phases of the illness could clearly be recognized—a period during which the symptomatology steadily worsened until a point of maximum intensity was reached, followed by a period in which no progression occurred. The period of time over which the illness worsened was quite inconstant; usually it was measured in weeks to months, but varied from as short a time as "overnight" to as long as 15 years. Despite the variablity in the tempo of evolution, it is particularly noteworthy that in all but a few of the patients the disease process ultimately stabilized. The data are probably less reliable in regard to the first phase of the illness than to the second. Many of the patients sought medical help only after their illness was fully developed, and the evidence pertaining to progression was mainly derived from their own observations. On the other hand, we feel entirely confident of the period of stabilization, since the data on this phase of the illness are derived from our own examinations, performed over a span of many years.

Our data do not provide a satisfactory explanation for this biphasic aspect of the illness. There is a suggestion that progression of the disease was associated with continued drinking and poor nutrition; and, conversely, that stabilization was associated with abstinence and improvement in nutrition. However, as has been pointed out in the clinical descriptions, this generalization must be qualified in several particulars: Six patients were actually abstinent at the onset of their illness; in one patient the disease appeared to have advanced in the face of reduction in alcoholic intake and improvement in nutrition; in five others it stabilized despite continued drinking and faulty nutrition. The causal role of alcohol and of malnutrition will be considered more fully in the discussion of etiology. It is safe to say, from our pathological findings, that only certain portions of the cerebellum are liable to involvement by this disease process; perhaps clinical stabilization simply reflects the fact that once these zones are affected, the disease does not spread beyond their boundaries. This is not a likely explanation in our cases, however, because all the patients did not stabilize at the same advanced stage of the disease. Entirely unanswered, of course, is the vital question of what renders these particular zones so susceptible to the degenerative process. There is no information available in medical writings to indicate that the region involved in this disease process can be separated from the remainder of the cerebellum by virtue of any unique enzymatic, biochemical, or pharmacological properties.

There were very few diseases, apart from other forms of cerebellar degeneration, which could be mistaken on clinical grounds for the disease under discussion. When the patient was seen for the first time, intoxication with alcohol, barbiturates, or diphenylhydantoin (Dilantin) had to be considered, since these states manifest themselves by a staggering gait and nystagmus. The problem of diagnosis resolved itself within a few days as the intoxicating

effects of the drugs wore off. In patients in whom alcohol or barbiturates had been withdrawn after a prolonged period of intoxication, there was a severe degree of weakness, tremor, difficulty in walking, and even nystagmus. The symptoms of the abstinence syndrome were quite distinctive, but here, again, the problem in diagnosis, if any existed, was resolved in a matter of a few days or a week, with recovery from the acute withdrawal effects. Wernicke's disease offered little difficulty in differential diagnosis in the fully developed form because of the prominent ocular palsies and overt disturbances of consciousness and mentality that consistently accompanied the ataxia. In a small number of cases, however, there were no abnormal mental signs; furthermore, during the phase of recovery, as the ocular palsies and confusion subsided, the nystagmus and ataxia of gait remained the prominent manifestations. It was under such circumstances that difficulty in diagnosis arose. In our experience the most useful point in differentiation is the fact that the ataxia of Wernicke's disease is limited to the function of stance and gait, and is not manifest during the individual movements of the legs.

In isolated circumstances, we had to consider the possibility of vascular disease (vertebral-basilar artery occlusion or midline cerebellar hemorrhage), neoplasm, and multiple sclerosis. The symmetry of the cerebellar signs, in our cases, as well as the lack of signs referable to the brain stem or other parts of the central nervous system and the absence of significant abnormalities in the spinal fluid, has served to set these cases of alcoholic cerebellar ataxia apart from the various forms of vascular, neoplastic, and demyelinative disease.

On purely clinical grounds, it was relatively simple to distinguish the disease under discussion from some forms of cerebellar or spinocerebellar degeneration and very difficult to distinguish it from others. Friedreich's disease and its variants are, of course, set apart by virtue of the early age of onset, the clear involvement of parts of the nervous system other than the cerebellum, the associated physical stigmata, and the familial history. So-called carcinomatous cerebellar degeneration was usually separable because of its steadily progressive course and because of the underlying carcinoma, and its relatively short duration (months or a year or two); also, diplopia is common, and often other parts of the neuromuscular system are affected. Olivopontocerebellar atrophy, in our opinion, could not be clearly distinguished on clinical grounds alone, despite the well-known coexistence of dementia, masked facies, muscular rigidity, incontinence, dysphagia, and loss of reflexes, which occur occasionally and which have been considered by some authors as distinctive features. The distinction between the disease under discussion and other forms of cortical cerebellar degeneration can be more effectively discussed after a consideration of the pathology.

B. Nature and Significance of Pathological Findings

1. *The Cerebellar Cortex.*—The essential pathological change, as seen in 11 cases with autopsy, was a degeneration of the cerebellar cortex, the most noteworthy features of which were the restricted topographical localization of the lesions and the consistency with which these changes reproduced themselves from case to case.

The superior vermis was involved in every case. The lingula and central lobule were affected in all cases and the culmen in all but one (Case 11). The next most frequently involved part was the declive (Cases 1-6, 8, 9), particularly those folia bordering upon the primary fissure. The rest of the vermis was involved much less consistently. The nodulus was affected in three cases (Cases 1, 2, 6), as was the pyramis (Cases 1, 2, 5), the uvula and folium were involved in two cases (Cases 1 and 2), and the tuber only in Case 1.

The hemispheres were involved less frequently than the superior vermis, and in a remarkably restricted fashion. In four cases (Cases 3, 4, 5, 9) the hemispheral affection was limited to the anterior lobes; in two others (Cases 1 and 2) the simple lobule, flocculus, and dorsal paraflocculus were also involved.

All elements of the cerebellar cortex partook of the disease process, although to a greatly varying extent. The most extreme change was seen in the culmen of Case 1; here the molecular layer was markedly reduced in width, with loss of all the nerve cell and fiber elements. The Purkinje cells were completely wiped out, and there was a severe loss of the nerve cells of the granular layer. There was a striking degree of fibrous gliosis throughout the cortex; the gliosis extended into the lamellar white matter, which was otherwise little affected. Cortical changes which were almost as severe as those just described were found in almost every case. In these somewhat less involved regions, the molecular layer was shrunken, and there was a partial loss of the nerve cells, and perhaps of fibers, in this layer. The Purkinje cells were nearly completely lost, although many empty pericellular baskets could be seen, and the granular cells were definitely reduced in number. Still less degrees of involvement were characterized by slight narrowing of the molecular layer and a severe degree of Purkinje-cell loss. The least discernible affection consisted of a partial loss of Purkinje-cells alone.

These varying degrees of affection of the cerebellar cortex, and their topography are represented in Figures 3-12, inclusive. The remarkable topographical restriction of the lesions to the anterior and superior portions of the vermis and the most anterior parts of the hemispheres is a matter which demands elaboration. It must be reemphasized that the disease process was not related primarily to accepted anatomical divsions of the cerebellum; that is, it did not respect the boundaries of specific anatomical lobes or lobules. Furthermore, the involvement of any given part was often incomplete or unequal; in fact, a patchy involvement was characteristic. It was frequently observed, for example, that the most superior portion of the declive, particularly those folia bordering on the primary fissure, were affected to a severe degree, whereas the more inferior parts of the same lobe were little affected, or completely spared. These points were strikingly illustrated by Case 2 (Fig. 4). Here the anterior portions of the anterior lobes were severely affected, the more posterior parts being less so. The simple lobules were severely involved in their paravermian distribution, but farther laterally the degree of affection of these lobules was considerably less. However, as one followed the process still more laterally, beyond the plane of the flocculus, very severe affection was once again detected in the simple lobules, as they took up a position along the anterior rim of the hemispheres. Thus, it would appear that the pathological process had struck the most anterior part of the hemispheres, regardless of the particular lobe or lobule which happened to protrude most anteriorly at any given point.

Just as this process bore no specific relationship to anatomical lobes or lobules as such, so it bore no relationship to the more general subdivisions based largely on comparative morphology. According to Larsell,[4,5] the cerebellum consists of two major components—the flocculonodular lobe and the corpus cerebelli. The corpus has been further divided into an anterior lobe (paleocerebellum) and a posterior lobe (neocerebellum). According to this classification, the anterior lobe comprises those vermian and hemispheral structures anterior to the primary fissure, and the posterior lobe, those structures between the primary fissure and the posterolateral fissure. It is apparent that in our cases the pathological alterations fell mainly within the anterior lobe, as defined by Larsell. However, except for Case 1, the entire anterior lobe

was not involved, and in many cases the involvement extended into the posterior lobe as well. Further, in Cases 1 and 2 the flocculonodular lobe was also affected, and in Case 6 the nodulus alone. Thus a precise relationship did not exist between the disease process and these general morphological subdivisions proposed by Larsell and others.

Jansen and Brodal,[10] Chambers and Sprague,[11] and others have suggested that the cerebellum may be divided, on the basis of its efferent connections, into three sagittally oriented portions—median (vermian), paramedian (paravermian), and lateral. Again, the disease process under discussion cannot be forced into any of these divisions, although the bulk of the lesion fell into the median one.

Jansen[12] has recently suggested yet another mode of divsion of the cerebellum, which combines the features of both the aforementioned classifications. He suggests that the cerebellum be parceled into "a series of transversely arranged lobules, some or possibly all of which are divisible into median (vermian), intermediate, and lateral parts." Even if one accepts this detailed arrangement, the problem of relating the disease process to the precise anatomical division remains unsolved.

At first glance, a topographical relationship seemingly exists between the distribution of the disease process and the areas which serve as the terminus for the ventral and dorsal spinocerebellar tracts and for the fibers derived from the external cuneate and paramedian reticular nuclei. However, the declive, inferior vermis, simple lobules, and flocculonodular lobe, all of which may be involved in this disease process, lie well beyond the confines of the sites of termination of these fibers, which are largely or entirely limited to the anterior lobe of Larsell.

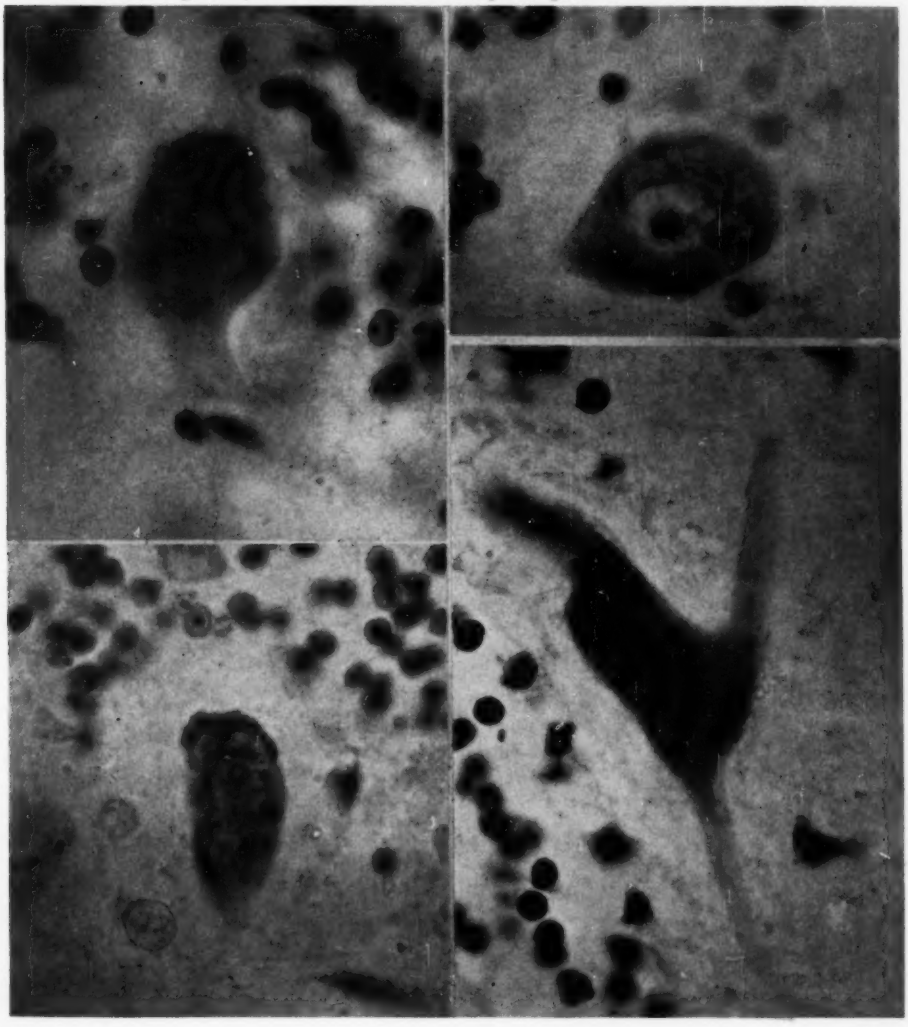
One has also to consider whether the cerebellar lesion in our cases falls within the territory of supply of any of the cerebellar arteries. It is true that the bulk of the lesion was found within the distribution of the superior cerebellar arteries. However, not all portions of the cerebellar cortex supplied by these vessels are affected (in particular, Crus I of the ansiform lobules and most of the anterior lobes and simple lobules); furthermore, much of the extracerebellar territory supplied by these vessels was completely spared (the superior and part of the middle cerebellar peduncles, and part of the pontine tegmentum). In addition, in at least some of the cases, affection was also present in regions of the cerebellar cortex supplied by both the anterior inferior and the posterior inferior cerebellar artery. The possibility, nonetheless, remains that some factor of circulation, e.g., richness of capillary supply, determined the localization of this disease.

It is commonly considered, in medical writings, that cerebellar degeneration of the general type under discussion is primarily or exclusively a Purkinje-cell disease. Such an idea is readily refuted by the examination of our material, which indicates that no single cell type is primarily involved. It is true that in the least severely affected portions only the Purkinje cells appeared to be lost. In the more severely affected regions, however, all neural elements, both cells and fibers in all layers of the cerebellar cortex, were seemingly equally affected. Not only were the Purkinje cells destroyed, but also, in varying degrees, the superficial stellate and basket cells of the molecular layer, the granule cells, and the Golgi II cells of the granular layer, as well as the multitude of nerve fibers of varying origin and termination found in all layers. If the Purkinje cells are the elements primarily involved, the degeneration of all the other elements would of necessity be largely retrograde in nature. Such a widespread affection is far beyond what could be expected on the basis of transsynaptic degeneration, as has been suggested. We must conclude that the affection is a zonal one, involving the cerebellar cortex in depth, as

a whole tissue, rather than one particular cell element therein. The fact that in some areas only the Purkinje cells are involved suggests that the disease struck here with less intensity and that the Purkinje cells, perhaps the most sensitive neural element in the cortex, were the only cells to become altered. It is well known that the Purkinje cells are particularly prone to be affected under certain conditions, e.g., anoxia or hyperthermia. In other words, the exclusive affection of Purkinje cells in the less involved regions may be regarded as a reflection of a similar "metabolic sensitivity."

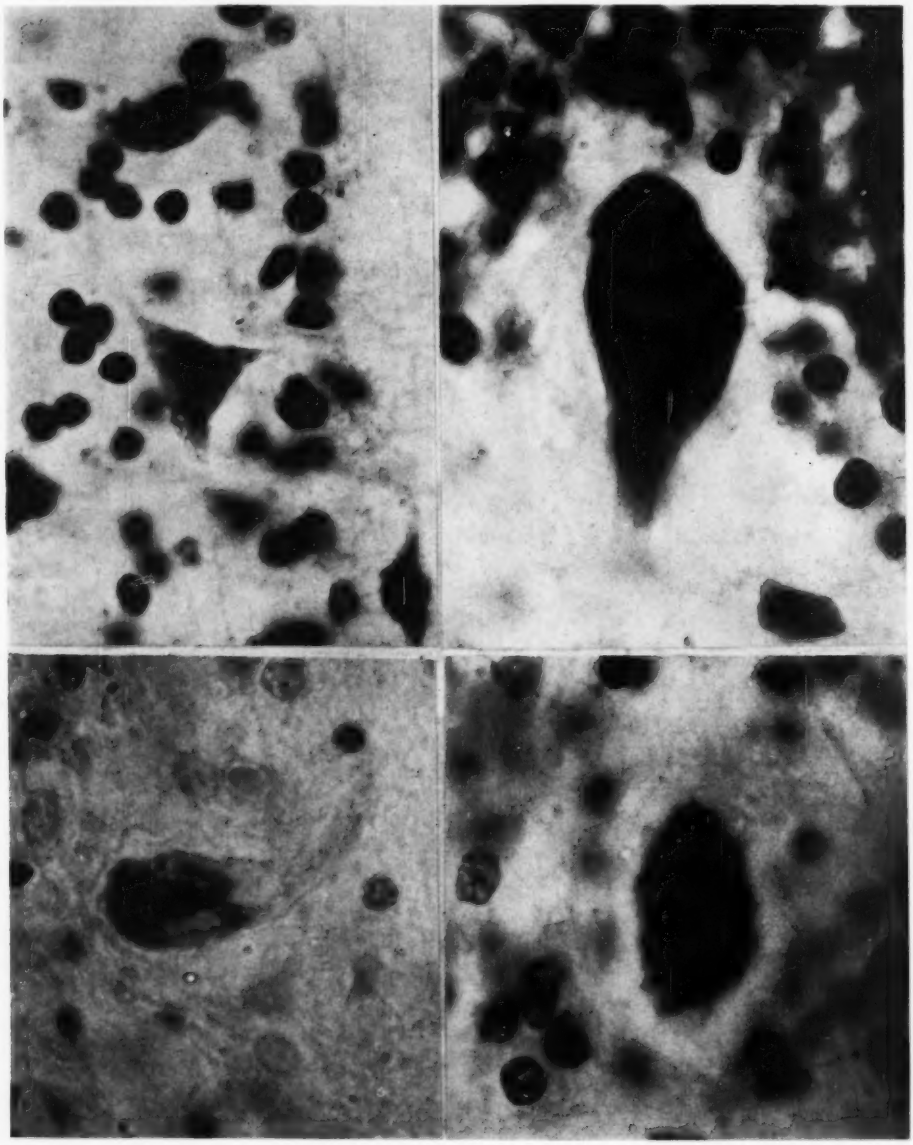
A number of less intense histopathological changes should be briefly commented upon. In the affected regions many of the remaining Purkinje cells were small. Such a change could simply represent shrinkage. However, as pointed out by Ramón y

Fig. 26.—Qualitative changes in Purkinje cells—swelling, indistinctness of nuclear membrane, perinuclear chromatin accumulation, and distortion of cell body. These changes, and those illustrated in Figure 27, were observed in both the pathological and the control material.



Cajal,[13] there is normally a wide variation in the size of Purkinje cells, from 35μ to 65μ in diameter; it is possible, therefore, that the remaining small cells were ones which were normally present and that they became conspicuous only after the larger cells had disappeared. Throughout the cerebellar cortex a variety of qualitative changes were observed in the Purkinje cells, such as pallor, swelling, pyknosis, indistinctness of nuclear membranes, perinuclear chromatin accumulation, and fray-

Fig. 27.—Further qualitative changes in Purkinje cells—shrinkage and pyknosis. (See also Figure 26.) Cresyl violet stain.



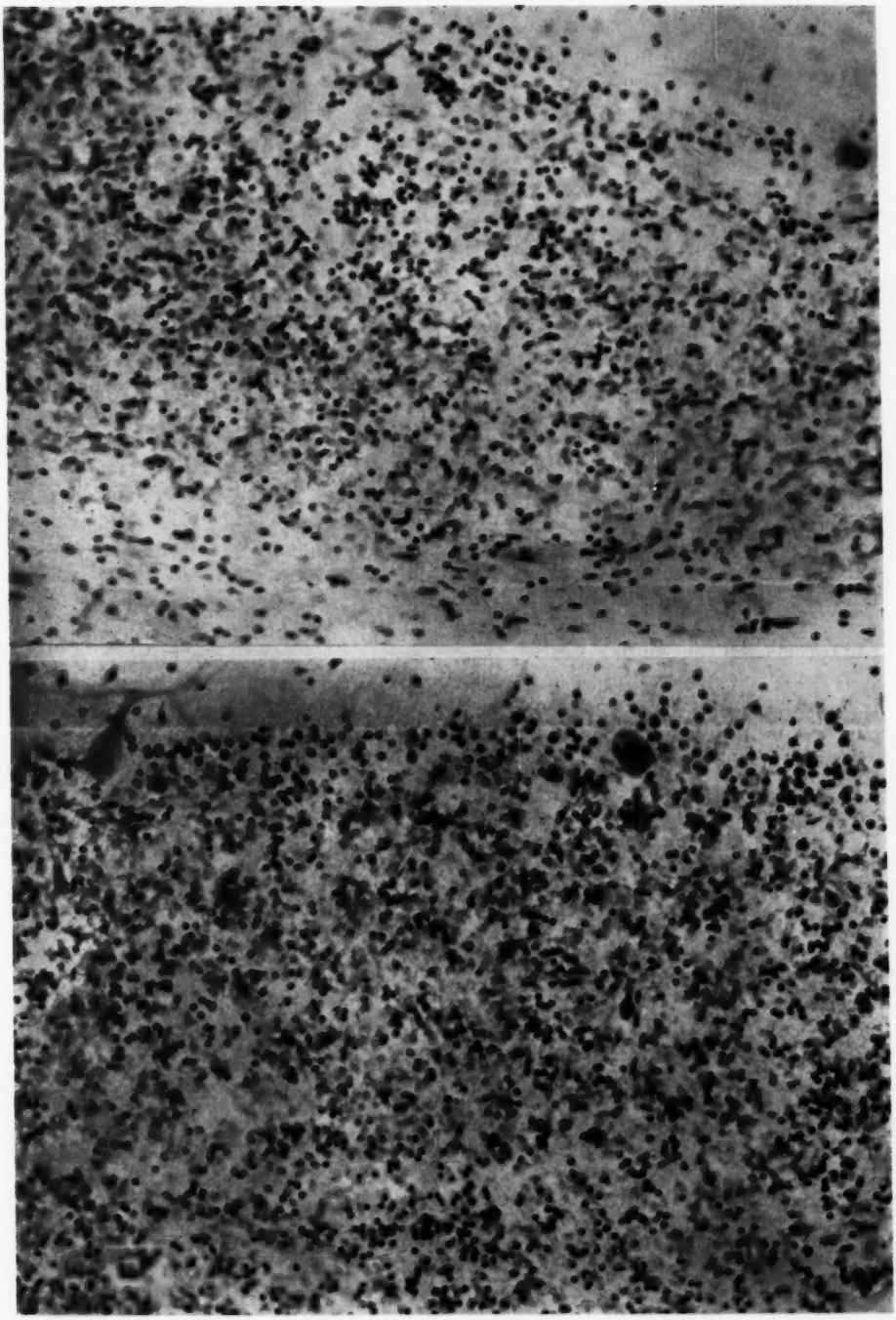


Figure 28.—Pallor of staining and conglutination of granule cells, as observed in control material. Cresyl violet stain.

ing of the cytoplasm. Such changes (which are illustrated in Figures 26 and 27) have often been taken as evidence of cellular disease. An attempt was made to evaluate these changes by comparing them with the appearance of Purkinje cells in control material, obtained from a group of patients, approximately of the same age as our own, who died of non-neurological causes. The tissue was preserved, embedded, sectioned, and stained in a manner identical with the tissue taken from the patients with cerebellar disease. The qualitative changes mentioned above were as frequently encountered in the control material as in the material taken from any of our patients. This was true whether one of the Nissl methods or Einarson's gallocyanin stain was used. We have been forced to conclude that these changes were either artifacts or agonal, and had little significance as reliable indicators of disease. However, since we were dealing here with a chronic disease process, we felt that only a definite loss of nerve cells was an acceptable criterion for the existence of the pathological process. All of our statements concerning the topography of the lesions have been based on this premise. Similarly, difficulties were encountered in evaluating the granule cells. Here, pallor of staining and conglutination have often been taken to represent disease of these cells. Again, by virtue of our observations on control material (Fig. 28), we are convinced that such alterations have no real significance, and that the only reliable change in regard to the granule cells is a reduction in their number, with an appropriate glial reaction.

The evaluation of the nerve fibers of the cerebellar cortex posed an especially difficult problem. The commonly employed methods of impregnation of axis cylinders (the Cajal reduced silver or one of the modifications of the Bielschowsky method) are notoriously capricious, so that an inability to visualize fibers did not necessarily mean that they had been lost. Even when the fibers were well impregnated, they were generally not revealed in their entirety, so that it was often difficult or impossible to establish their specific nature. The problem was made even more difficult by the bewildering variety of nerve fibers in the cerebellar cortex. The more prominent fiber components, such as the Purkinje dendrites and axons and the peri-Purkinje basket formations, were readily recognized by use of the usual impregnation methods. However, these methods were not always satisfactory for the identification of other fiber components, such as the mossy and climbing fibers, T-axons of granule cells, basket fibers, and recurrent collaterals of Purkinje axons. These considerations have prompted us to be cautious in the interpretation of the state of the nerve fibers in our cases and in the acceptance of the findings reported by others, based on the same impregnation techniques.

A final comment should be made about the peri-Purkinje basket formations. Many writers have emphasized that these structures are preserved in degenerative diseases of the cerebellar cortex and have often remarked that the constituent fibers are thickened and "hypertrophied." In general, the pericellular baskets were preserved in our cases. However, even these structures were destroyed in the most intensely affected regions (the culmen of Case 1), and their preservation, therefore, cannot be considered as an invariable feature of this disease. In the affected regions the constituent fibers of the baskets were more heavily impregnated than usual. One cannot infer that they were necessarily "hypertrophied," since the heavy impregnation may simply reflect a local alteration in staining properties. Furthermore, in some cases, the fibrils making up the baskets appeared fine and regular and did not differ from those seen in the control material.

The type of glial response in these cases was characteristic of a chronic disease process; i.e., it was predominantly astrocytic with the elaboration of a dense glial fibrillar network. Generally this gliosis was iso-

morphic, but in the most severely affected part (the superior culmen of Case 1) a dense anisomorphic gliosis was seen, the glial fibrils mingling with proliferated adventitial fibers to produce striking glial-vascular whorls (Fig. 14*B*). In no case was there a prominence of fat-laden macrophages, although here and there one observed a sprinkling of these cells, containing fine sudanophilic droplets, in the cerebellar cortex. In several cases small clusters of 5 or 10 pleomorphic microglia cells were seen in and just above the Purkinje cell layer; they were probably tiny "glial bushes," indicating a recent or continuing degeneration of the Purkinje elements.

2. *The Cerebellar White Matter.*—Fibrous gliosis was present in the lamellar, but not in the central, white matter of the cerebellum. In the lamellar white matter, the proportion of the Purkinje axons to other fibers is greater than in the central white matter, a fact which probably explains why gliosis was demonstrable only in the former structure. Alterations in the floccular peduncles and in the medial fastigiobulbar tracts were clearly recognizable in Cases 1, 2, and 5.

3. *The Deep Cerebellar Nuclei and Associated Structures.*—In no case was the dentate nucleus seriously depleted of nerve cells. A mild patchy loss of cells in these nuclei was present in Cases 1, 6, and 9. In these cases, and in several others, there was also a mild diffuse astrocytic hyperplasia. In addition, there was (in Cases 2 and 3) a microglial proliferation in the most medial and anterior portions of the dentate nuclei. The emboliform and globose nuclei were most severely affected in Case 1, and to a less severe extent in Case 2; here, there was a loss of nerve cells and proliferation of astrocytes and microglia cells. In Cases 3 and 5 the nerve cells appeared intact, although similar glial changes were seen. The fastigial nuclei showed a severe loss of nerve cells only in Case 1. In Cases 2, 4, 6, and 9 the abnormality consisted of varying degrees of astrocytic and microglial proliferation, the nerve-cell population being intact.

According to Jansen,[14] it is generally accepted that the corticonuclear projections of the cerebellum can be divided into three zones: (1) The Purkinje-cell axons from the vermis terminate in the fastigial nuclei; (2) those from the paravermian cortex terminate in the globose and in the emboliform nuclei, and (3) those from the lateral portions of the hemispheres (excluding the flocculus) project to the dentate nuclei. The histopathological finding in our cases would tend to support this proposition, providing that one accepts microglial and astrocytic proliferation in the absence of nerve-cell loss as indicative of secondary degeneration. The fastigial nuclei were affected in those cases of ours with the most extensive and severest alterations in the vermis; conversely, these nuclei appeared intact where the vermis lesion was most restricted. In all cases in which the globose and emboliform nuclei were affected, there was involvement of the paravermian portions of the hemispheres, and in only one case (Case 9) was there involvement of the paravermian cortex without appropriate changes in these nuclei. These corticonuclear relationships were least convincing in respect to the dentate nuclei. In Cases 2 and 3 the focal changes in the dentate nuclei were probably related to the degeneration in the anterolateral portions of the anterior lobes; however, in Cases 1, 4, 5, and 9, in which the anterolateral portions of the anterior lobes were also involved, no focal changes in the dentate nuclei were apparent.

The olives were affected, at least to some extent, in all but two cases (Cases 7 and 11). In six cases (Cases 1, 3, 4, 5, 6, and 8) the affection was severe in degree and involved the dorsal laminae of the inferior olives, particularly in their most medial folds, and most of the dorsal accessory olives. The medial accessory olives were diffusely involved in Case 8, and in three

other cases (Cases 1, 2, and 6) only their dorsal portions were involved. A precise statement regarding olivocerebellar relationships cannot be made on the basis of our material, since the olivary complex was not studied in serial section. In general, however, our findings are in keeping with those recently summarized by Brodal.[15] Thus, the changes in the dorsal accessory olives were probably secondary to the degeneration in the superior vermis, those in the medial accessory olives being due to a degeneration in the inferior vermis (an exception being found in Case 8); and the changes in the dorsal lamina of the inferior olives were probably related to the degeneration in the dorsal hemispheres (an exception was our Case 6). The affection of the medial portion of the dorsal lamina of the inferior olive was probably due to the relatively greater affection of the paravermian portions of the hemispheres.

Although the topographical relationship between the olives and the cerebellar cortex has been appreciated since the studies of Holmes and Stewart,[16] a satisfactory explanation of the olivary degeneration secondary to disease of the cerebellar cortex has not been forthcoming. The commonly held view that the olivary change represents a transsynaptic degeneration due to Purkinje-cell loss appears most unlikely, since such a degeneration would have to take place across two synapses (i.e., Purkinje cells to granule cells to olivary cells) and in a retrograde direction. However, the point has repeatedly been made that in the disease under discussion all elements of the cerebellar cortex are affected rather than Purkinje cells alone, and it would therefore be more logical to regard the olivary-cell changes as secondary to the involvement of their terminations as mossy fibers in the granular layer.

The changes in the vestibular nuclei were difficult to assess, but these nuclei appeared to be involved in five cases (1, 2, 4, 5, and 6). The superior nucleus (Bechterew) was affected in all but Case 2; the spinal nucleus was involved in Cases 1 and 2, and the medial and lateral nuclei in Case 1 only. The significance of these changes was difficult to evaluate. Even in these cases, in which all the nuclei could be identified with certainty, there was no uniformity of involvement. It would thus be unlikely that the changes were primary in the vestibular complex; rather, they were probably secondary to the alterations of the cerebellar cortex. Whether these secondary changes resulted from the loss of Purkinje cells which project directly to these nuclei or from disease of the terminals of the vestibulocerebellar fibers was impossible to judge. The absence of axonal reaction in the vestibular nuclei could not be considered decisive because of the chronicity of the process.

The ventral spinocerebellar tracts were involved only in Case 2, and only in their retro-olivary portions. In all the other cases the spinocerebellar tracts, as well as Clarke's columns, were intact. The nerve cells of the basis pontis were present in normal numbers except for Case 1, and here the loss was of a random nature and mild in degree. The plump astrocytes seen in some of the cases probably reflected the presence of advanced liver disease. The nucleus reticularis tegmenti pontis (of Bechterew), whose fibers project to the vermis, was the seat of an intense fibrous gliosis in Case 2, but was not affected in any of the other cases. Also in Case 2, some of the nerve cells of the motor nucleus of the fifth nerve were altered; the significance of this change is obscure, since the precise relations between the trigeminal complex and the cerebellum are not clear. In Cases 2 and 6, changes suggestive of "axonal reaction" were seen in the nucleus gigantocellularis, and in the former case the same type of change was also detected in the nucleus paragigantocellularis lateralis and nucleus of the pallidus raphe. These changes are of doubtful significance, since they may normally be seen in these nuclei, as pointed out by Olszewski and Baxter.[6]

All the other nuclear masses of the brain stem considered to have either an efferent or an afferent connection with the cerebellum were normal. There was mild pallor of myelin staining in the central portion of the inferior cerebellar peduncles in Cases 1 and 6, accompanied, in the latter case, by mild fibrous gliosis. The middle and superior cerebellar peduncles were well myelinated, but there was often a slight astrocytic hyperplasia in these structures, as though some fiber loss had occurred, perhaps secondary to the cell loss in the roof nuclei. The meninges of the posterior fossa were not remarkable in any of our cases.

The blood vessels, both meningeal and parenchymal, showed no consistent changes; all were patent, and their walls were only hyperplastic to a mild or moderate degree in a few instances. In two cases (Cases 5 and 10) ferruginization (pseudocalcification) was present in the walls of arterioles in or near the dentate nuclei. This finding appeared to be of no particular significance, and simply reflected a more generalized, banal hyperplastic arteriosclerosis. In no case were inflammatory changes noted.

4. *Associated Disease Processes.*—There were a number of significant pathological changes in the nervous system apart from those in the cerebellum and its immediate connections. Five patients had evidence of polyneuropathy (Cases 1-5). Case 3, moreover, also showed degenerative changes in both optic nerves and tracts restricted to the zone of the papillomacular bundles; this lesion was consistent with the clinical state of deficiency amblyopia. In Cases 1, 6, 7, and 8 there were lesions characteristic of long-standing Wernicke's disease. In must be significant that all of these associated diseases are generally conceded to be nutritional in origin. The finding of the lesions of Wernicke's disease in four of our patients raises the problem of the relationship between the two diseases, a matter which will be considered later, in "Comment."

In addition, five patients (Cases 1 to 4, and 9) and perhaps another (Case 10) showed a change considered by Adams and Foley to be characteristic of hepatic encephalopathy, viz., diffuse hyperplasia and hypertrophy of protoplasmic astrocytes.[17] It is noteworthy that all but one of these five patients died of liver coma. This astrocytosis was often a source of difficulty in evaluating the presence of disease in the deep cerebellar, vestibular, and other nuclei of the brain stem.

5. *Importance of Studying the Cerebellum in the Sagittal Plane in Cases of Alcoholic Cerebellar Degeneration.*—An important lesson to be derived from this study concerns the purely practical matter of how best to process the cerebellum. We urge that the cerebellum be sectioned in the sagittal plane, the initial cut being made in the midline through the vermis. Only in this way can one be certain not to miss mild, or even moderately advanced, instances of this disease. The reason for this statement is apparent when one considers the remarkably restricted topography of the lesion. It is true that in Case 1 the changes were readily discerned in horizontal section, but this represented our most extensively involved case. In the less extensively involved cases the most anterior and superior folia of the vermis and hemispheres would have been missed in horizontal sections, unless the cerebellum were serially sectioned in this plane. An additional advantage to be gained from sagittal section concerns the identification of the component parts of the cerebellum and the assessment of the individual cortical elements. Both of these tasks are more readily accomplished by the study of sections cut in this plane.

C. Clinical Pathological Correlation

Perhaps the most important aspect of this study concerns the relation of the clinical to the pathological findings, as well as the inferences to be derived from such a correlation concerning the functional or-

ganization of the cerebellum. Attempting to deduce such relationships, it is to be noted that certain features of our case material were particularly advantageous—the chronicity of the disease process, the long periods of clinical stability, the stereotyped character of both the clinical and the pathological findings, and the sharp restriction of the lesions.

The topography of the cerebellar cortical lesions and their varying severity have already been discussed in detail and are graphically portrayed in Figures 3 to 12. The relation between the clinical and the pathological findings is most readily discerned by referring to these diagrams. A number of important facts become evident. Concerning the topography of the lesion and its clinical manifestations, it appears that there was a wide variation among cases. At one end of the scale are the patients (e.g., Case 11) who had no signs of cerebellar disease during life and yet showed a lesion of the cerebellar cortex postmortem. Here the lesions were restricted to the lingula and central lobule and, as would be expected, were relatively mild in degree. In several other patients (e.g., Cases 7 and 8) the clinical abnormality took the form of a slow, wide-based, unsteady gait, individual movements of the limbs being unimpaired. Here the pathological process involved all of the superior vermis but was particularly severe in the lingula and central lobule. In the cases which were characterized by an ataxia of the legs and arms, as well as of gait, the clinical-pathological correlation was less exact. In Case 1, for example, the lesions were widespread, involving not only the superior vermis and anterior lobes but also the posterior vermis, lobulus simplex, flocculus, nodulus, and vestibular nuclei. Case 5, on the other hand, which was also distinguished clinically by an ataxia of gait, legs, and arms, showed lesions only in the superior vermis and anterior lobes. These findings would indicate that the lesions in this portion of the cerebellum, i.e., the superior vermis and anterior lobes, are responsible for the syndrome of ataxia of gait and the legs and, to a less extent, of the arms. The findings in Cases 3 and 4, in which the lesions were also of this restricted nature, would warrant the same conclusions.

The pathological basis for nystagmus and speech disturbance could not be determined from our material. In Cases 1 and 2, which showed the most widespread lesions, there were no abnormalities of speech. Yet this function was affected in Cases 4 and 5, in which the lesions were limited to the superior vermis and anterior lobes. Similarly, nystagmus was present in Case 4, in which the lesions were of the restricted variety. The presence of nystagmus could not be attributed to extracerebellar lesions, such as those of Wernicke's disease. In two patients with nystagmus (Cases 2 and 4) no Wernicke lesions were present. Furthermore, in two of the four patients with Wernicke's disease (Cases 6 and 7) no nystagmus had been detected.

The functional capacities of various parts of the cerebellum, as deduced from these observations, are not in keeping with many of the prevailing concepts of the functional organization of this organ, such as those described by Fulton and Connor.[18] On the basis of the anatomical subdivisions proposed by Larsell,[4] these authors have delineated three major cerebellar syndromes: (1) the syndrome of the posterior lobe, or the neocerebellar syndrome, which is characterized by disturbances in the rate, force, direction, and range of volitional movements, without affecting equilibrium per se; (2) the syndrome of the flocculonodular lobe, characterized by a disturbance of equilibrium, individual movements of the extremities being unaffected, and (3) the syndrome of the anterior lobe, or the paleocerebellar syndrome, in which disturbances in the postural sphere, increased tendon reflexes, pronounced lengthening and shortening reactions, and gross exaggeration of

positive supporting reactions are the outstanding features.

Little can be deduced from our case material about the function of the posterior lobe, since this portion of the cerebellum was virtually unaffected. However, the distribution of the lesions in our cases does allow us to make some critical comments on the so-called syndromes of the flocculonodular lobe and the anterior lobe.

It would appear from the animal experiments of Dow [19] and of Carrea and Mettler [20] that the isolated ablation of the flocculonodular lobe results in conspicuous disturbances of equilibrium but leaves unimpaired the volitional movement of the limbs. There is no conclusive evidence, however, that these findings pertain in man. The literature contains repeated reference to analogous clinical situations induced by certain tumors of childhood, namely, the medulloblastomas.[21-23] In the course of this tumor growth, there may indeed exist a disturbance of gait and equilibrium, without tremor or ataxia of the individual movements of the arms and legs, so long as the patient is lying still. Since these tumors allegedly originate from cell rests in the posterior medullary velum at the base of the nodulus, it has been inferred that these clinical symptoms result from the involvement of this portion of the cerebellum.[24,25] The validity of this deduction remains to be proved, for when these tumors are inspected at operation or autopsy they have spread far beyond the confines of the nodulus and no reliable clinical-pathological correlation can be made.

Our own case material does not support the idea that the flocculonodular lobe is essential for the maintenance of equilibrium. In three cases (Cases 1, 2, 6) the flocculonodular lobe was involved entirely or in part, and it is possible that this lesion added to the severity of the gait disturbance. In the other eight cases, however, the flocculonodular lobe was entirely unaffected and thus could not be implicated in the clinical picture. It is of particular interest that in Cases 7 and 8, in which the clinical abnormality was limited to a disorder of stance and gait, there was no affection of the nodulus or flocculus.

The evidence for the existence of an anterior lobe (or paleocerebellar) syndrome in man, as proposed by Brown [26] or by Bailey,[22] is tenuous, to say the least. Each of these authors, as well as Kononova,[27] has described a group of symptoms resulting from an invasive tumor in this general region. The selective involvement of the anterior lobe must, under such circumstances, remain in doubt. It is a fact that in all our cases the bulk of the lesion was located anterior to the primary fissure, and in many cases the lesion was confined to this territory. In this respect, our cases, and similar ones reported in the literature (Table 5), are more representative of the "anterior lobe" syndrome than the ones based on tumor pathology. Our objections to the use of this designation have been pointed out: The lesions do not conform precisely to what has been defined anatomically as the anterior lobe or physiologically as the paleocerebellum.

The symptoms seen in our patients bore little resemblance to those described by Fulton and Connor as the syndrome of the anterior lobe.[18] We were unable to demonstrate the postural abnormalities, increased tendon reflexes, exaggerated supporting reactions, and increased shortening and lengthening reactions seen by these authors in primates. On the other hand, the relation between the clinical and the pathological findings in our cases is particularly meaningful in the light of more recent concepts of the functional organization of the cerebellum. These new ideas have been reviewed in detail by Henneman [28] and by Dow and Moruzzi [29] and will be referred to here only in the briefest terms. These authors point out that sensory impulses of all types project to the cerebellum. Tactile stimulation,[30] proprioceptive stimulation,[31] and stimulation of peripheral nerves [32] all evoke potentials which can be recorded

from the cerebellar cortex. A mapping of these evoked potentials has demonstrated a consistent somatotopic localization in the cerebellar cortex. Motor effects produced by stimulation of specific areas in the cerebellar cortex[32,34] have demonstrated a similar localization, as have the ablation experiments of Carrea and Mettler.[20] From these data there has been postulated in the experimental animal a body scheme with topographical representation of specific bodily parts in the cerebellar cortex. The tail is represented in the lingula, the lower extremities in the central lobule and its extensions into the more anterior folia of the anterior lobes, the arms in the culmen and the more posterior parts of the anterior lobes, and the head and neck in the declive and simple lobules. Although, in general, the trunk appears to be represented in the medial parts of these subdivisions and the extremities in the lateral, there is no reason, from this experimental work, to ascribe separate functions to the vermis and the hemispheres. Instead, each subdivision of the vermis and its contiguous hemispheral portions represents a functional unit. Of considerable interest is a "secondary" topographical representation in the pyramidoparamedian complex on each side. These relationships are diagrammatically portrayed in Figure 29, which has been adapted from Snider.[35]

This physiological and anatomical formulation would explain most of the findings in our cases, for the regions of the cerebellum most frequently affected were the lingula, the central lobules and the most anterior folia of the anterior lobes, the culmen (but not its hemispheric portion), and the declive (the last in a varying, and usually in a restricted, manner). It is apparent that the "leg area" in the experimental animal corresponded with the area consistently involved by the pathological process in the human cases, viz., the central lobule and the most anterior folia of the anterior lobes. One is immediately drawn to the conclusion that this feature explains the ataxia of gait and incoordination of the legs, which were the most prominent clinical features in all our cases. Although the culmen was also frequently affected, its lateral extensions into the more posterior folia of the anterior lobes were spared (with the exception of Case 1). Thus, much of the experimentally demonstrated "arm area" was uninvolved; as a corollary, the arms were only slightly affected in the majority of the cases. Again, the declive was involved in varying degree in eight of the cases, but its hemispheral parts—the

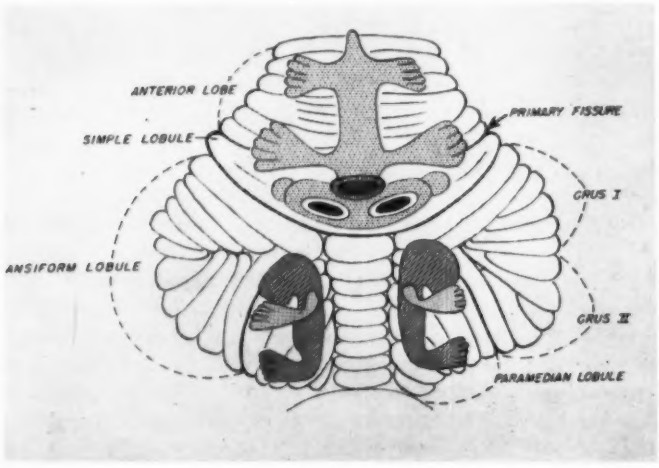


Fig. 29. — Somatotopic localization in the cerebellar cortex. Adapted from illustration in article entitled "Interrelations of Cerebellum and Brain Stem," by R. S. Snider (*A. Res. Nerv. & Ment. Dis., Proc.* 30:267, 1950), by permission of the publishers, Williams & Wilkins Company, Baltimore.

simple lobules—were affected in only two, and even in these cases only the paravermian portions were seriously altered. Thus, the bulk of the region considered representative of the head and neck was spared, and, indeed, aside from an inconstant and minimal dysarthria, there were no clinical signs referable to this zone.

It is of added interest that the site of the secondary topographical representation, i.e., the pyramidoparamedian complex, was largely spared. The paramedian lobule was not affected in any one of our cases, and the pyramis was involved in only three of them, but only to a slight degree. Perhaps the sparing of this area, as well as the minor affection of the deep nuclei, explains the fact that the clinical disability was not total; most of the patients still retained sufficient control of their legs to get about.

There is as yet no conclusive evidence as to the site of the lesions responsible for nystagmus or for ocular dysmetria. Our own data shed no light on this problem. Also, the pathological basis for the unusual static tremor could not be determined from our material, since none of the patients who showed this symptom came to autopsy.

D. Etiological Considerations

A large number of factors of possible etiological significance were suggested by the case histories and examinations, but only a few of these need to be considered seriously. Plumbism, pulmonary tuberculosis, syphilis, head trauma, carcinoma, pneumonia, and influenza had all occurred in isolated cases. Three cases of influenza, two of syphilis, and one each of tuberculosis and plumbism had all occurred many years before the onset of cerebellar symptoms, and on this basis alone could probably be considered to have no etiological relationship. One patient had serologically positive syphilis when his cerebellar signs were first discovered; but there was no evidence, clinical or pathological, that he had neurosyphilis. In another patient fibrocaseous tuberculosis was recognized shortly after the onset of cerebellar symptoms, both illnesses developing on a background of chronic undernutrition. In two patients cerebellar ataxia became evident immediately following an attack of lobar pneumonia, although the fever in these cases was only moderate in degree. One patient (pathological Case 6) was found to have carcinoma of the larynx several months after the onset of a cerebellar syndrome; in this case the pathological changes were restricted to the superior vermis, and in our minds this feature alone clearly separated it from "carcinomatous cerebellar degeneration." As will be pointed out later, the cerebellar degeneration associated with carcinoma is characterized by a much more widespread involvement of the cortex than was encountered in this patient.

The serious abuse of alcohol was a feature common to all our patients, and one's first inclination is to ascribe the cerebellar disease to the direct toxic effect of alcohol itself. It is noteworthy, however, that in six patients there was a history of abstinence from alcohol for varying periods of time before the onset of their cerebellar disease. Although the reliability of such a history could be doubted, the evidence for abstinence was considered incontrovertible in at least three of these patients who were under close supervision in a hospital when cerebellar disease developed. It is manifestly difficult under such circumstances to accept the toxic effect of alcohol as the direct causative agent.

The other feature which demands consideration in regard to etiology is the role of nutritional deficiency. As indicated previously, evidence gleaned from the history and examination indicated that fully three-quarters of the patients suffered from chronic undernutrition. It was of particular interest that in eight of these patients an extreme degree of weight loss had occurred just prior to the onset of cerebellar symptoms. Furthermore, one cannot assume that the remaining patients were well nourished at the time of onset of their

cerebellar disease, since many of them first came to our attention many years after the onset of this illness, that is, after a long period of abstinence and concomitant improvement in their eating habits.

A number of reports in the medical literature may have a bearing on the nutritional aspect of the etiology. Stannus [36] described a child with recurrent pellagra who also showed a fluctuating cerebellar syndrome. Ransome,[37] commenting on this report, cited his experience with a series of 18 cases of pellagra which occurred in Singapore in 1940-1941, many of which showed a gross cerebellar syndrome. Danaraj [38] described the case of an elderly Chinese man who developed progressive cerebellar signs on a background of severe nutritional deficiency; the neurological signs disappeared within three months after the institution of a liberal diet plus nicotinic acid and riboflavin. The patient of Houssiau [39] developed a transient cerebellar syndrome following a period of severe vomiting and weight loss associated with amebiasis. All of these cases appear to be acceptable as clinical examples of cerebellar disease, particularly since there were no signs of polyneuropathy or posterior-column affection in any of them. However, in none of these cases was the lesion verified pathologically.

There are remarkably few accounts of nutritionally induced changes of the cerebellum in the experimental animal. Miyagawa [40] and Swank and Prados [41] reported fragmentation and irregular thickening of fiber systems of the cerebellar cortex in thiamine-deficient pigeons, but such findings in themselves are difficult to interpret. Pappenheimer and Goettsch [42] produced a cerebellar disorder in chicks by the administration of a diet consisting of milk powder, starch, cod liver oil, salts, filter paper, and dried baker's yeast. The lesions in the cerebellum were crude and widespread, consisting of edema, necrosis, and hemorrhage. Although these lesions probably resulted from nutritional deficiency, it does not appear justified to attribute them to a specific lack of vitamin E. Lhermitte, Ajuriaguerra, and Garnier [43] described the occurrence of chromatolysis and extreme pallor of the Purkinje cells of rabbits who were fed alcohol for a period of several weeks; these changes were reportedly not seen in animals who had received supplemental thiamine. This work suffers from the fact that the lesions were not illustrated; under any circumstances, the changes described in the Purkinje cells were entirely qualitative ones, and, as has repeatedly been stressed, slight cell alterations of this type must be interpreted with caution.

Many toxic and metabolic agents have been incriminated in the production of cerebellar cortical lesions. Since none seems to have a direct bearing on our cases, they need be considered only briefly. Of these, the best known is anoxia. Interestingly, the changes in the cerebellum in anoxic encephalopathy are generally severest in the depths of the sulci, a change quite the reverse of that seen in our material. Also, the anoxic lesions are not restricted to the parts of the cerebellum involved in the alcoholic patient. A loss of Purkinje cells, gliosis, and possible rarefaction of granule cells may occur as a result of hyperthermia,[44-46] but in these circumstances the affect is always a diffuse rather than a restricted one.

Of the toxic agents, lead has been invoked by de Villaverde [47] and by Ferraro and Hernández [48] as a cause of cerebellar degeneration. The basis for such statements rests entirely on one's interpretation of qualitative changes of the Purkinje cells, variously described as the acute or severe cell change of Nissl. In a report of a patient who had died of lead poisoning, Freifeld [49] made brief reference to an actual loss of Purkinje cells. Hunter, Bomford, and Russell [50] described four cases of poisoning due to the inhalation of methyl mercury compounds, in which cerebellar signs were prominent. Hunter and Rus-

sell [51] performed a pathological examination of one of these patients and reported a severe loss of granule and Golgi II cells, most marked in the hemispheres, the Purkinje cells being relatively well preserved; there was also an extensive loss of the fiber systems of the cerebellar cortex. These authors [50] claimed to have produced a similar lesion in rats exposed to methyl mercury but were unable to produce this change in monkeys. Upners [52] described focal granule-cell changes and severe loss of all cortical elements in the cerebellum of dogs poisoned with thiophene; the preponderance in the vermis of lesions from the latter source was of particular interest. The toxic effects of prolonged ingestion of DDT (chlorophenothane) on dogs has been described by Haymaker, Ginzler, and Ferguson.[53] Even in those animals which received the largest doses for the longest period of time, the major changes consisted of pyknosis or pallor of the Purkinje cells, with only a minimal reduction in their number and with no concomitant gliosis. An instance of possible human DDT poisoning has been reported by Shanks and Elliott.[54] Here, again, the pathological changes in the Purkinje cells were essentially qualitative ones, despite the fact that symptoms of incoordination, dysarthria, involuntary movements, and weakness had existed for 14 weeks before death. Stevens and Forster [55] reported the case of an alcoholic patient who died seven days after acute intoxication with carbon tetrachloride. They described a marked reduction in number of both Purkinje cells and nerve cells of the molecular layer without gliosis; however, their illustration of this change is not convincing. Baker and Tichy [56] and Baker [57] described both qualitative and quantitative changes in the Purkinje cells in experimental intoxication with a variety of organic solvents, including toluene, ethyl acetate, and trichloroethylene. Similar lesions have been reported in dogs which were fed nitrogen chloride (Agene), a substance which at one time was used to bleach wheat flour.[58,59] Calcification in the granule-cell layer has been found by Noetzel [60] and Enders and Noetzel [61] in rats poisoned with mercury bichloride; since there were no other consistent pathological changes in the cerebellum, the significance of these observations is obscure. Van Bogaert and Dallemagne,[62,63] in their studies on experimental manganese intoxication, described not only qualitative changes in, but also a frank loss of, Purkinje cells. The case reported by Hofmann,[64] in which cerebellar degeneration followed the administration of exceedingly high dosage of diphenylhydantoin (Dilantin) is difficult to judge and may represent an instance of anoxic damage to the cerebellum.

The so-called Gordon phenomenon, i.e., the degeneration of Purkinje cells in experimental animals following the injection of eosinophils (reviewed by Meyer and Foley [65]), most likely bears no relationship to the cerebellar degeneration under discussion. Recently Alajouanine et al.[66] have given a clinical account of two patients who showed an eosinophilia associated with pulmonary infiltrates and a cerebellar syndrome; possibly the Gordon phenomenon was of some significance here. In our cases, however, no eosinophilia was encountered. Indeed, in only one pathologically verified case of cerebellar degeneration in the medical literature, that reported by Barraquer-Bordas and Ruiz-Lara,[67] was even a moderate degree of eosinophilia described.

Repeated reference is made in the medical literature to "premature senility" of the cerebellar cortex, as though this term in itself was capable of explaining the type of cerebellar degeneration under discussion. Our own observations are of some interest in this regard (Table 4). Although we have observed some loss of Purkinje cells in old age, this loss, even in a 90-year-old man, was much less severe than that observed in any of our pathological cases. Furthermore, the loss of Purkinje cells in the elderly was a generalized one, showing none

of the topographical restriction which was so characteristic of the cases of cerebellar degeneration. In this respect, as has been pointed out, our observations are not in agreement with those of Ellis.[8] It has also been our observation that in senility the pathological change in the cerebellar cortex was essentially one of Purkinje cells, whereas in the cases of cerebellar degeneration all the cortical elements could be affected. For all these reasons, one cannot accept the idea that a process of premature aging is responsible for the restricted type of cerebellar degeneration seen in the alcoholic patient.

The contention that the disease under discussion results from the action of any one of a number of "toxic" agents upon a congenitally "weak" or defective cerebellar cortex is purely speculative and can be neither proved nor disproved. The major obstacle to the acceptance of such an idea is our inability to judge the presence of such a "weak" cerebellum on either pathological or clinical grounds. In none of our cases did the full-blown cerebellar syndrome develop on a background of mild cerebellar symptoms or signs which dated from earliest childhood—if such signs can be taken to represent the presence of a "weak" or defective cerebellum. Indeed, in our review of the literature, we have been able to uncover only three cases in which signs of cerebellar disease were present from earliest childhood and worsened later in life; these were the cases of Zülch (Case 2),[68] of Morsier and van Bogaert,[69] and of Fattovich.[70] Similarly, there is no way of proving or disproving the contention that long-standing alcoholism renders the cerebellum vulnerable to an otherwise innocuous illness, e.g., pneumonia, although a number of our patients developed their symptoms under just such circumstances.

E. Review of the Medical Literature

It is interesting now to view this clinicopathological entity against the background of all the proved examples of cortical cerebellar atrophy. This enables us to ascertain its specificity as a pathological process and indicates the major gaps in our knowledge. An attempt has been made to review as completely as possible the medical writings dealing with cerebellar atrophy or degeneration. This has proved to be a difficult undertaking. It soon became obvious that only pathologically verified instances of cerebellar disease lent themselves to analysis, since on clinical grounds alone it was quite impossible to be certain of the type of cerebellar involvement, or, indeed, whether the cerebellum was involved at all. Even in those instances in which the pathology was described, many inadequacies were encountered: scant historical data, lack of attention to the family history, incomplete general and neurological examinations, inadequate descriptions of the topographical and histopathological features of the cerebellar lesions, a failure to describe the remainder of the nervous system, etc. In some cases, these defects were serious enough to preclude a clear definition of the disease process, and, in consequence, their proper categorization.

The following analysis is concerned only with the *pathologically verified cases of cerebellar degeneration in which the disease process is limited to or predominant in the cerebellar cortex*. Excluded are the many disease processes in which the cerebellar cortex may be secondarily involved. Focal disorders of the cerebellum, such as tumor, infarctions, and the common demyelinative processes, are therefore not included. The same applies to instances of infectious disease which were said to affect the cerebellar cortex, such as the cases of syphilitic meningoencephalitis reported by Bielschowsky and Hirschfeld[71] and by Alajouanine and Hornet,[72] and the case of tuberculous meningitis described by Pollak,[73] as well as to other bacterial and viral encephalitides. Although the cerebellar cortex may be involved in some instances of olivopontocerebellar atrophy, as pointed out by Scherer,[74] Critchley and Greenfield,[75] and Brouwer

and Biemond,[76] this disease seems to be a distinct pathological entity, affecting predominantly the basis pontis, the middle cerebellar peduncles, and the central cerebellar white matter, and therefore differing from the primary cortical degenerations. The same reasoning prompted us to exclude those examples of Friedreich's disease in which the cerebellar cortex was also affected,[77-79] of congenital aplasia or hypoplasia of the cerebellum,[80] and of crossed cerebrocerebellar degeneration, recently reviewed by Verhaart and van Wieringen-Rauws.[81] Also excluded is the curious form of focal panatrophy of the cerebellar cortex, which is usually asymptomatic and found incidentally at autopsy. This has variously been described as cortical cerebellar atrophy without ataxia by Lichtenstein and Levinson,[82] as sclerotic atrophy of the cerebellum by Hassin,[83] and as lamellar sclerosis by Hanón.[84] The so-called bibasal marginal atrophy of Jakob[85] possibly represents the same process.

We also feel justified in excluding those disease processes in which the cerebellar lesion is but a fragment of a widespread affection of the nervous system. The most readily recognized of these are anoxia and hyperthermia. Less common examples are Jakob-Creutzfeld disease,[86] the infantile form of diffuse cerebral degeneration of Alpers,[87,88] cerebral lipoidoses,[89,90] and Hallervorden-Spatz disease.[91-93] Instances of leukodystrophy in which the cerebellar cortex is involved secondarily to the white matter[94-97] were treated in the same way, as were the isolated reports of cerebellar cortical affection in Wilson's disease,[98] in tuberous sclerosis,[99,100] and perhaps in mongolism.[101]

With the exclusion of these various forms of cerebellar disease, we were left with 120 pathologically verified cases of cerebellar degeneration in which the disease process was limited to or predominant in the cerebellar cortex. The main features of these cases have been summarized in tabular form (Tables 5-10). Two cases have not been included in this summary—the case of Marie, Foix, and Alajouanine, Case 5,[107] and that of Scherer,[102] since no clinical information of any kind accompanied the pathological reports. From the over-all group, it has been possible to derive at least five subdivisions, each with distinctive clinical and pathological features.

1. Sporadic cases beginning in adult life, on a background of prolonged alcoholism, characterized clinically by a chronic course, usually with long periods of stability, and pathologically by a predominance of the degenerative changes in the anterior superior vermis and hemispheres
2. Sporadic cases occurring in adult life, associated with carcinoma, characterized clinically by a subacute, steadily progressive course, and pathologically by diffuse and approximately equal degenerative changes in all portions of the cerebellar cortex
3. Sporadic cases beginning in infancy and childhood, usually progressive and associated with mental retardation, characterized pathologically by diffuse changes in the cerebellar cortex, generally severer in the hemispheres, and by lesions in other parts of the central nervous system
4. Heredofamilial cases of cortical cerebellar degeneration
5. Cases characterized pathologically by a selective degeneration of the granule-cell layer and clinically by an onset in infancy or childhood and by mental retardation
6. Miscellaneous cases

Tables 5-10, summarizing the cases in the medical literature, have been drawn up in accordance with this classification. Each of these categories will be commented on briefly.

Group 1. *Sporadic cases beginning in adult life, on a background of prolonged alcoholism, characterized clinically by a chronic course, usually with long periods of stability, and pathologically by a predominance of the degenerative changes in the anterior superior vermis and hemispheres*[103-114]

This group comprises 11 cases, but the restriction to this number is arbitrary. Most likely the case reported by Rossi[174] belongs in this group but was not included because no mention is made of the patient's

TABLE 5.—*Pathologically Verified Cases of Cortical*

Sporadic Cases Beginning in Adult Life on Background of Prolonged Alcoholism, Characterized Clinically by Chronic Course, and Hemispheres

Author	Sex	Age of Onset, Yr.	Duration, Yr.	Mode of Evolution	Associated Conditions	Symptoms: Ataxia: Gait	Ataxia: Legs	Ataxia: Arms
Thomas[100]	F	40	19	Slowly progressive 14 yr.; stable 5 yr.	Severe alc.; chr. pulmonary disease	+++	+++	+
Jakob[104]	M	61	11	Slowly progressive	Severe alc. and malnutrition	++++	+++	+
Lhermitte[105,106]	M	66	13	Minimal signs 12 yr.; rapid progression several mo.; stable at least 6 mo.	Severe alc.; malnutrition; Ca pancreas	+++	+++	0
Marie, Foix, & Alajouanine[107] Case 2		62	6	Very slowly progressive	Severe alc.	+++	++	±
Kufs[108]	M	42	9	Progressive 2 yr. (?); stable 7 yr.	Severe alc.; syphilis	+++	+++	0
Stender and Lüthy[109]	M	60	16	Rapid evolution; stable 15 yr.	Severe alc.; polyneuropathy	+++	+++	++
Noica, Nicolesco, and Hornet[110]	M	24	4	Rapid evolution; stable 4 yr.	Moderately severe alc.; onset after head injury; pulmonary tbc.	+++	0	+
de Haene[111]	M	59	18	Progressive 6 mo.; stable 7 yr.; slowly progressive 10 yr.	Severe alc.	+++	+++	+
Guillain, Bertrand, & Guillain[113]	M	44	8	Slowly progressive 2 yr.; stable, or only slightly progressive, 6 yr.	Severe alc.	++++	++	++
Guillain, Bertrand, & Guillain,[113]	M	42	25	Stable 12 yr.; progressive 3 yr.; stable 10 yr.	Severe alc.; chronic plumbism	++++	++++	+++
von Santha[114]	M	36			Severe alc.; malnutrition; chronic gastritis	++++	+++	+

Cerebellar Degeneration in the Medical Literature

Usually with Long Periods of Stability, and Pathologically by Predominance of Degenerative Changes in Anterior Superior Vermis

and Signs			Pathological Changes				
Dysarthria	Nystagmus	Others	Cerebellar Cortex	Deep Cerebellar Nuclei	Olives	Other Parts CNS	Comment
+	+	Hypotonia; bilat. extensor plantars	Sup. vermis most affected			Sclerosis ant. horns lumbosacral cord	
+	0	Hypotonia; ment. deterior. chron. auditory, hallucinosis (?)	Vermis much more than hemispheres	0	0	Senile changes cerebral cortex	
0	0		Sup. vermis, ant. lobes, simple lobules	0	0		
0	0		Nearly confined to sup. vermis and ant. lobes	Fastig. fleece +	0		
0		Hypalgesia legs	Severest sup. vermis, ant. lobes, simple lobules; much less severe in rest of cortex	Dent. +	+	Syphilitic meningoencephalitis	Definite evidence of CNS syphilis only 8½ yr. after onset of cerebellar disease
++	0	Polyneuropathy	Severest in culmen, declive, folium, ant. lobes, simple lobules; somewhat less in lingula central lobule; rest much less affected	0	+	Senile atrophy cerebral cortex	
++	+	Hypotonia	Severest paleocerebellum; neocerebellum much less affected	Dent. +	+	Inf. cerebellar peduncle; direct spinocerebellar tr.; temp. pontine tr.	
+	+	Vertigo, cong. abducens palsy	Severest sup. vermis, ant. lobes, simple lobules; less severe in inf. vermis, crus I, flocculi, dors. paraflocc.; rest little affected	Dent. fleece ±	+	Hypoplasia, left abducens nucleus	
++	+	Hypotonia; static tremor arms	Severest culmen, declive, ant. lobes, simple lobules; rest little affected	Dent. +	+		
	+	Vertigo; hypotonia	Severe in culmen, declive, central lobule; less severe in ant. lobe, simple lobule; flocculus severe; post. and inf. parts slightly affected	Dent. ±	+	Small temporal infarcts	
±	0	Emaciation, D.T.'s; polyneur	Severest in lingula, central lobule, culmen, sup. declive, pyramis; less severe in paravermian portions of ant. lobes, simple lobules	0	+	Wernicke's dis. moderate cerebral atrophy	

TABLE 6.—*Pathologically Verified Cases of Cortical*

Sporadic Cases Occurring in Adult Life Associated with Carcinoma, Characterized Clinically by Subacute, Steadily Progressive

Author	Sex	Age of Onset, Yr.	Duration, Yr.	Mode of Evolution	Associated Conditions	Symptoms: Ataxia: Gait	Ataxia: Legs	Ataxia: Arms
Brouwer[115]	F	60	½	Progressive	"Polymorphic-cell sarcoma of pelvis"	++++	++++	+++
Casper[116]	F	43	¼	Progressive	Ca breast	+++	+++	+++
Parker and Kernohan[117]	F	56	2¼	Progressive	Ca ovary	++++	+++	+++
Greenfield[118] Case 1	F	66	¼	Progressive	"Tumor of Breast"		+	++
Case 2	M	57	½	Progressive	Ca lung	+++	+++	0
Kennard[119]	F	59	1½	Progressive	Ca ovary	++++	+++	++
Zülch[44] Case 1	F	50	1½	Progressive	Ca ovary	++++	+++	+++
Kecht[120]	F	50	?¼	Progressive	Ca ovary	+++		
Alessi[121]	F	40	⅜	Abrupt onset ? progressive	Ca uterus	++++	++++	+++
Brouwer and Schlesinger[122]	F	51	1	Progressive	Ca ovary	+++	+++	+++
Zülch[123] Case "Dunk"	F	66	1½	Progressive	Ca cervix	+++	+++	+++
Brain, Daniel, & Greenfield[124] Case 1	F	61	¼	Progressive	Ca ovary	++++	+++	+
Case 3	F	54	¼	Progressive	Ca lung	+++	++	++

Course, and Pathologically by Diffuse and Approximately Equal Degenerative Changes in All Portions of Cerebellar Cortex

and Signs			Pathological Changes				
Dysarthria	Nystagmus	Others	Cerebellar Cortex	Deep Cerebellar Nuclei	Olives	Other Parts CNS	Comment
+++	+	CSF normal	Probably generalized	Dent. fleece +	0		
++	++	Diplopia, dysphagia, absent A.J.'s; CSF normal	Generalized	Dent. +	0	Degen. column of Goll	
++	0	Coll. gold curve 5544410000	Probably generalized	0			
++	+	Hypotonia; bilat. ext. plantars; poor memory; CSF: 30 lymphs; prot. 100 mg. %; coll. gold 555555443	Generalized	0	0	Degen. subthal. nucl. strio-Luysial fibers, post. roots, long tracts of cord, Gower's tract in medulla	Perivasc. and meningeal inflammatory
±	0	Pains, parathesias, hyporeflexia, bilat. ext. plantars; dement; CSF: 113 lymphs, prot. 450 mg. %, coll. gold 0000122112	Generalized; (?) vermis somewhat more than hemispheres	Dent. +	0	Degen. subthal. nucl., glob. pall. Clarke's column, long tracts of cord, vestib. efferent fibers, sup. cerebellar peduncle	Perivascular inflammatory cells
+++	+	Tinnitus, vertigo, deafness, diplopia, blurred vision; coll. gold 2223211100	Generalized	Dent. + Embol. + Glob. + Fastig. +	0		
+++	++	Diplopia, catalepsy, static tremor, forced grasping, bilat. ext. plantars; coll. gold 454321111	Generalized	Dent. fleece +	0	Nonsystemized degen. all tracts of cord	
++		Pyramidal signs; CSF: paretic curve	Generalized				
	++	Vertigo, "ocular myoclonus," hypotonia, postural tremor; CSF normal	Generalized	Dent. fleece +	0		
++	++	Diplopia, dizziness, hypotonia; coll. gold 444333100	Generalized	Dent. +; dent. fleece + Embol. + Glob. + Fastig. +	0	Vestib. nucl.; left sup. cerebellar peduncle	Perivascular and meningeal inflammatory cells
++	0	Dementia, tremor head	Generalized except (?) lat. parts hemispheres	0	0		
+++	+	Diplopia, dementia; CSF: 48 lymphs, prot. 100 mg. %, coll. gold 5555421100	Generalized		0	Degen. pyramidal, dors. spinocerebellar tracts	Perivascular inflammatory exudate in cerebellum
+++	++	Skew deviation, CSF bloody, prot. 150 mg. %; coll. gold normal	Probably generalized	+		Degen. spinocerebellar tracts, dorsal columns	Perivascular inflammatory exudate in cerebellum

TABLE 6.—Continued

Barraquer-Bordas & Ruiz-Lara[87,188]	M	70	1	Progressive	Ca lung	++++	++++	+++
Henson, Russell, & Wilkinson[124] Case 5	F	47	2½	Progressive	Ca ovary	+++	+++	+++
Case records of Massachusetts General Hospital[116]	F	34	1¾	Progressive	Ca breast	++++	++++	+++
Malamud[117]	M	45	1½	Progressive	Hodgkin's disease	++++	+++	+++

alcoholic habits; nevertheless, the patient died of cirrhosis of the liver with ascites, and the clinical and pathological features are identical with others in this group. It is probable that the first three cases of Ohkuma[182] also belong in this category, since the patients were all severe alcoholics who showed the lesions of Wernicke's encephalopathy. However, they were placed in the miscellaneous group because of the lack of data concerning the topography of the cerebellar lesions, as was Case 3 of Feizullaev and Sukhova.[206]

It is apparent from an inspection of Table 5 that the cases in this group bear a remarkable resemblance to our own. Of the 11 patients, 10 were men. All of them were undoubted alcoholics, and the presence of malnutrition was specifically noted in three. The average age of onset of the cerebellar symptoms was 48.7 years, and the average duration of the disease was 13 years. The course of the illness was characterized by long periods of stability in eight cases, and was said to be slowly progressive in only two. In all patients the most prominent neurological abnormality was the ataxia of gait and the legs; the affection of the arms was always relatively less, and only in the one case of Guillain, Bertrand, and Guillain[113] could it be considered severe in degree. Nystagmus, dysarthria, and hypotonia were less consistent signs, each being present in five instances. The pathological changes were also remarkably similar to those observed in our cases. In each instance the cerebellar cortex was involved and the lesions were restricted to the anterior-superior parts of the vermis and hemispheres. Reference to alterations in the dentate nucleus was made in only two instances; the myelin sheaths surrounding the fastigial nuclei were affected in one case; the olivary complex was affected in seven cases, probably reflecting the chronicity of the disease process.

The case of Lhermitte[105,106] requires a word of qualification. The patient died of carcinoma of the pancreas, and the question arises as to whether or not the cerebellar disease was related to the malignancy rather than to alcoholism. Probably it was not, since the cerebellar symptoms preceded the recognition of the neoplasm by over 12 years; furthermore, all the clinical and pathological features in this case are of the type encountered in the alcoholic group, and different from those of the carcinomatous one (see below). For a similar reason, we feel that the carcinoma of the larynx in our pathological Case 6 was not causally related to the cerebellar syndrome.

TABLE 6.—Continued

+++	+	Diplopia, hypotonia, hyporeflexia, forced crying, incontinence	Probably generalized	Dent. fleece + Dent. + Embol.+ Glob. + Fastig. +	+	Degen. vestib. aud. pontobulbar nucl., nucl. of solitary tr., trapezoid body, descend. root V and post. col.; cerebral metastases	Perivascular inflammatory cells
++	+	Diplopia, resting tremor head & legs; CSF: 11 lymphs, prot. 40 mg. % coll. gold 012221	Generalized	Dent. fleece +	0		? Myopathy
++	++	Dizziness, weakness, oscillopsia, abs. A.J.'s bilat. ext. plantars; CSF normal	Generalized	Dent. fleece +	0	Degen. corticospinal & spinocerebellar tr., columns of Goll	
+++			Generalized				Hodgkins disease of spleen, lymph nodes and bone marrow

Group 2. *Sporadic cases occurring in adult life, associated with carcinoma, characterized clinically by a subacute, steadily progressive course, and pathologically by diffuse and approximately equal degenerative changes in all portions of the cerebellar cortex*[67,68,115-127]

It was somewhat surprising that only 17 pathologically verified instances of this type of cerebellar degeneration could be found in medical writings. In all likelihood, Case 1 of Henson, Russell, and Wilkinson,[125] Case 4 of Brain, Daniel, and Greenfield,[124] and one of the cases described by Malamud[127] belong in this group. In the first of these patients there was a carcinoma of the breast, and in the other two, carcinoma of the lung; they were placed in the miscellaneous group because the authors provided no information as to the topography of the lesions in the cerebellar cortex.

In this group the cerebellar degeneration was associated with carcinoma of the breast and of the lung in three patients each. Two patients had a carcinoma of the uterus, and one, a "polymorphic cell sarcoma of the pelvis." In almost every respect the clinical and pathological features of this group are in striking contrast to those in Group 1. Of the 17 cases in Group 2, 14 were women. The average age of onset of cerebellar symptoms was 54. The duration of the cerebellar disease was two and a half years in the longest instance (Case 5 of Henson, Russell, and Wilkinson[125]). Of the 17 patients, 10 lived for only a year or less after their cerebellar symptoms became manifest. The cerebellar symptoms were invariably progressive, with the possible exception of one case.[121] In all cases, ataxia of gait and of the legs was a prominent finding, but, in contrast to Group 1, the arms were also severely affected in 13 of the 17 cases. Similarly, a severe disorder of speech was noted in 15 cases, and nystagmus in 12 cases. Hypotonia was found in five cases. Although remission in symptoms has not been a feature in this group of pathologically verified cases, recent clinical experience suggests that such may occur,[128] or that the complaint may become arrested short of complete disablement.[129]

A number of neurological signs, not ordinarily regarded as cerebellar in nature, and spinal fluid abnormalities were frequently encountered in these patients—features which served to sharpen the contrast with the alcoholic cases. Thus, eight patients complained of diplopia, and two others had abnormalities of ocular motility ("ocular myoclonus," oscillopsia). In four

patients vertigo or dizziness was a major complaint. Pyramidal tract signs were observed in five cases; dementia, in three, and a pseudobulbar phenomenon, in one. The spinal fluid was examined in 14 cases but was completely normal in only 3. The most frequent abnormality (seven cases) was a first-zone colloidal gold curve. An elevated spinal fluid protein, as high as 450 mg. % (Case 2 of Greenfield[118]), was recorded in four instances and a mild lymphocytosis in three.

The pathological changes were also distinctly different from those of Group 1, particularly in regard to the topography of the lesions. In contrast to the sharp restriction of the lesions in the alcoholic cases, the changes were more or less equal throughout the cerebellar cortex in the carcinomatous cases. The rapid evolution of the cerebellar disease was reflected histologically by the signs of an active destructive process, i.e., by the prominent microglial activity, the presence of fat-laden macrophages, and the frequent occurrence of perivascular and meningeal inflammatory exudates. The last-mentioned change, in our opinion, is probably a secondary or reactive one, and should not be taken to indicate an infectious etiology. Brouwer and Biemond[76] believe that the climbing fibers are preserved in the generalized form of cerebellar degeneration and that these fibers are lost in the localized form. We are reluctant to accept this as a significant distinguishing feature, because, as has been pointed out, we have found it most difficult to judge with assurance the state of the cortical fiber systems. Affection of the deep cerebellar nuclei was much commoner in the carcinomatous than in the alcoholic cases. A more arresting difference between the two groups was in the state of the olivary complex, which was considered normal in all but one of the carcinomatous cases. Finally, the involvement of nerve roots, the spinal cord, and the various brain-stem and basal-nuclear structures was commonplace in the carcinomatous cases, in contrast to the alcoholic ones.

It will be noted that in the miscellaneous cases of cerebellar degeneration (Table 10) there are included four instances in which a carcinoma was present.[194,195,199,202] These cases were excluded from Group 2, since the malignancy was detected many years after the onset of the cerebellar symptoms; furthermore, in all but one of these cases[199] the pathological changes were of the localized type. Also excluded from the carcinomatous group was the case of Kecht and Pollak,[130] in which the cerebellar syndrome had its onset two years after an operation for carcinoma of the ovary, and in which there were no lesions in the cerebellar cortex, the main affection being one of the cerebellar white matter.

Group 3. *Sporadic cases beginning in infancy and childhood, usually associated with mental retardation, characterized pathologically by diffuse changes in the cerebellar cortex, often severer in the hemispheres, and by lesions in other parts of the central nervous system* †

This group presented the greatest problem in regard to the selection of cases, mainly because of the difficulty, recognized by many of the authors of these cases, in separating hypoplasia of the cerebellum from acquired degeneration in infancy and childhood. We finally selected 15 cases which were thought to represent instances of degeneration, although even in some of these there may have been a combination of hypoplasia and a superimposed degenerative process. This group may have been further adulterated by the inclusion of cases in which anoxic damage to the cerebellum had occurred at birth or in earliest infancy. Judging from the histories of these cases, the possibility of an early anoxic episode was not always considered, nor does the pathological examination of the cerebellum, performed years later, always allow an accurate reconstruction of events to be made. A case in point is that

† References 33, 68-70, 77, 102, 114, 131-137.

of Scherer (Case 1936),[102] in which the cerebellar disease was directly related to the occurrence of a widespread and severe encephalitis in childhood.

Of the 15 patients, 8 were female and 5 male, and in 2 the sex was not stated. The course of the illness was variable: In six, or perhaps seven, patients it was steadily progressive, and in three it was stationary, or nearly so, for many years, only to worsen late in life. In five cases the natural history of the illness was not clearly described.

The most striking clinical feature of this group was the high incidence of mental retardation, which was present in at least 10 of the patients. Recurrent seizures had occurred in two patients; transient diabetes and ovarian atrophy, in one each. The clinical data in these cases are insufficient to allow a characterization of the cerebellar syndrome which would be applicable to the group as a whole. In at least two instances[69,132] there were few, if any, cerebellar signs during life. In several others there was a severe ataxia of gait and of individual movements of the legs; in some instances the arms and speech were also severely affected. Hypotonia was observed in three patients. Nystagmus was found in only one of the patients, but ocular palsies were mentioned in three. As can be discerned from Table 7, this group was characterized by the presence of a wide range of neurological abnormalities, in addition to the cerebellar ones; and this feature had its counterpart in the widespread pathological changes in the nervous system.

The topography of the lesions in the cerebellar cortex was not uniform. In 10 of the 14 cases in which the topography was described, the changes were diffuse; in 4 of these the alterations were severer in the hemispheres than in the vermis; in 3 the opposite was true, and in the 3 others the changes were apparently equal throughout the cerebellum. In three cases only the hemispheres were affected; in one case the lesions were of the restricted variety, much as in our Group 1. The deep cerebellar nuclei were affected in 8 cases, and the olives in at least 11. The high incidence of involvement of the olives, as in Group 1, probably reflected the chronicity of the disease process.

Group 4. *Heredofamilial cases of cortical cerebellar degeneration*

This group included 26 cases occurring in 23 families and consisted of 19 males and 7 females. Here, also, there was a problem in delineating the precise bounds of the group. It seemed logical to exclude those unusual familial instances of cerebellar disease characterized by a specific degeneration of the granule cells (see below). In general, cases of Friedreich's ataxia have been excluded, for reasons that have already been given; however, the case of Crouzon and Bertrand[148] has been included because the diagnosis of Friedreich's disease cannot be definitely made in this instance. Some of the cases which we have designated as "sporadic" could conceivably have been heredofamilial in nature, since a complete family history was not provided. However, we cannot agree with Richter[145] that "parenchymatous cortical cerebellar atrophy is in fact a primary heredo-familial degeneration," since in many cases a detailed family history clearly excluded a hereditary or familial aspect, and other exogenic factors are now known to affect the cerebellum.

Nine patients developed cerebellar symptoms in infancy and childhood, and seventeen, in adult life. The average age of onset of the latter group was 45.6 years, with a range of 28 to 70 years. The course of the illness was chronic and steadily progressive; the only exceptions to this rule were the cases of Akelaitis,[141] in which death occurred within two years of the onset of the cerebellar disease, and the cases of van Bogaert[144] and Crouzon and Bertrand,[148] in which there were long periods of stability. No single mode of inheritance could be discerned; examples of dominant, recessive, and sex-linked inheritance were all encountered. In 5 of the 26 cases, hypogen-

TABLE 7.—*Pathologically Verified Cases of Cortical*

Sporadic Cases Beginning in Infancy and Childhood, Usually Progressive and Associated with Mental Retardation, Characterized Nervous System

Author	Sex	Age of Onset, Yr.	Duration, Yr.	Mode of Evolution	Associated Conditions	Symptoms: Ataxia		
						Gait	Legs	Arms
Vogt & Astwazaturow[77] Case 4	M	8	21	Progressive	Ment. retard.; fits; pulm. tbc.	+++		
Case 5	M	3	43	Progressive	Ment. retard.	+++		++
Schob[181]	F	infancy	50+	Progressive		+++	+++	+++
von Santha[88]	F	infancy		Progressive	Ment. retard.	+++	+++	+++
Scherer[183] Case FA 256/29		?infancy			Idiocy			
Case 1936		infancy	2		Ment. retard.			
Zülch[88] Case 2	F	earliest childhood	50+	Worse in late 40's	Ment. retard.	++++		
Morsier and van Bogaert[89]	F	8	56	Unchanged until last yr. of life	Transient diabetes; splenic cholesterosis			
Norman[185]	M	?1	?33		Mental and physical retardation	0	0	0
Minogue and Latham[186]	F	9	9	Rapid onset; course unknown	Seizures	+++		
Grisoni[184]	M	less than 3	3-4	? Progressive	General retard.	++++	+++	+++

Cerebellar Degeneration in the Medical Literature

Pathologically by Diffuse Changes in Cerebellar Cortex, Generally Severer in Hemispheres, and by Lesions in Other Parts of the

and Signs			Pathological Changes				
Dysarthria	Nystagmus	Others	Cerebellar Cortex	Deep Cerebellar Nuclei	Olives	Other Parts CNS	Comment
+	0	Titubation head; converg. strabismus; asymmetry cranium	? Hemispheres particularly affected	Dent. fleece + Roof nuclei +	+	Degen. ext. cuneate nucl.	Basal parts of laminae more severely affected than distal
++		Malnourished, grimacing; increased muscle tone; Parkinson tremor	Topography not described				2 nephews imbeciles
++	±	Inact. pupils; absent knee and ankle jerks	Hemispheres more affected than vermis; flocculi least	Dent. fleece +	+	Degen. post. columns, Lissauer's tr., Clarke's column, tr. solitarius	Considered cong. syphilis clinically
++	+	Vertigo, bilat. VI nucl. palsy, color blind, concent. narrowing of visual fields, chorea, loss position and reflexes in legs	Hemispheres more affected than vermis; vermis more than flocculi	0	+	Defective gyral pattern; loss cortical nerve cells, atrophy nucl. Goll, Burdach; thinning Helwig's tr.; diplomyelia, (?) ganglion-cell tumors cauda equina	Cousin midget; mentally retarded
			Hemispheres most affected; flocculi and vermis relatively preserved	Dent. fleece +	+	Hydrocephalus; atrophy striatum, thal. minimal loss cells, pontine nuclei	Cerebellum very small
		Cachexia; areflexia; agonal fits	Similar to previous case	Dent. fleece +	+		Several neonatal episodes of asphyxia and hypotonia
++		Athetosis toes; bilat. ext. plantars	Sup. vermis most affected, then sup. hemispheres, inf. hemispheres and least inferior vermis	Dent. fleece +	0		
	0	Flexor and tonic spasms; myoclonus; memory loss	Probably generalized	0	0	Atrophy striatum, glob. pall., subthal. nucl.; gliosis sup. cerebellar ped.	Clinically an extrapyramidal syndrome with few cerebellar signs
0	0	Spasticity	Severest in hemispheres; vermis and flocculus hardly affected	0	+	"État marbré" caudate, nucleus, putamen, and thal.; gliosis, glob. pall. substentia nigra; brain wt. 1,151 gm.	
		Dementia; spastic paraplegia	Generalized; most intense in culmen, declive	0	0	Brain wt. 1,020 gm.	Cerebellum wt. 96 gm.
++	0	"Spastic hypotonia"; pendular K.J.'s; CSF probably normal	Hemispheres more affected than vermis and flocculi	Embol. + Glob. + Fastig. +	+	Atrophy arcuate nucl.	

TABLE 7.—Continued

André-van Leeuwen and van Bogaert[105] Case "Frey"	F	9		Progressive, acute worsening in year before death, due to medullary infarction	tbc.; ovarian atrophy; (?) ment. retard.	+++	+++	+++
van Bogaert et al.[105]	F	3	2+	Progressive		Cerebellar signs early		
Hagen, Noad, and Latham[147]	M	?	?73		Ment. retard.	++	++	++
Fattovich[79]	F	?infancy	?80	Stable until age 66; then progressive	Ment. retard.; poor nutrition	+++		

italism was a prominent feature; in 3 other instances, recently described by Boder and Sedgwick[157,158] and by Biemond,[163] a curious combination of bronchiectasis and oculocutaneous telangiectasia was present. Epilepsy was present in three cases; macular degeneration and neurofibromatosis were each present in one case.

We have arbitrarily divided the heredofamilial cases on the basis of the topography of the cerebellar lesions. In nine cases the lesions were restricted in a manner similar to that seen in the sporadic alcoholic cases. In 12 other cases the lesions were generalized and about equal in all portions of the cerebellar cortex. In the remaining five cases the lesions were also generalized but unequal, the hemispheres in general being more severely affected than the vermis. The term "Holmes type" has been used indiscriminately to designate all type of familial cerebellar degeneration, perhaps because the case of Holmes[139] was the first to be adequately described. Actually the term is applicable only to the first of the aforementioned groups, since the pathological changes in Holmes' case were restricted—to the vermis and anterior parts of the hemispheres, the flocculi, and those parts of the inferior olives which are anatomically related to the degenerated cerebellar cortex.

It is our impression that the cerebellar signs were somewhat different, depending upon the topographical distribution of the lesions. Where the pathological changes were largely restricted to the anterior superior portion of the vermis and hemispheres, the arms tended to be less affected than the legs and the gait. In the cases with diffuse pathological changes, the affection of the arms and of speech function was perhaps more prominent.

In the entire group, seven cases showed hypotonia. The same number had nystagmus, and, in addition, two cases had ocular dysmetria, two had abducens palsy, and one each had paralysis of conjugate gaze, macular degeneration, and optic atrophy. Extrapyramidal signs, including rigidity, choreoathetosis, and Parkinsonism were found in 10 patients; pyramidal tract signs were present in 3 others; myoclonus, of an unspecified type, was said to be present

TABLE 7.—Continued

+++		Hypotonia; loss position sense; acrocyanosis; deformity foot; optic atrophy; CSF normal	Generalized; vent. parafloc. less affected than remainder	Dent. + Embol. + Glob. + Fastig. +	+	Atrophy, pallidum, subthal. nucl., red nucl. ant. horns, post. columns, spinocerebellar tr.; gliosis, thal.; degen. papillomacular bundles	
		Later choreoathetosis; extensor spasms; dystonia	Generalized; sup. more than inf. vermis	Dent. + Roof +	+	Atrophy pallidoLuysian system, red nucl., nucl. of post. column, olfactory system, sup. olives, retic. formation, vestib. nucl., centrum ovale, post. columns and roots; pallor, pyramidal tr.	
++		Ocular palsy; cataracts; scoliosis	Generalized	0	+	Senile changes, cerebral cort.; retinitis pigmentosa	Cerebellum weight 46.5 gm.
+	0	Senile dementia, hypotonia	Generalized; severest sup. vermis; focal meningocerebellar scarring	0		Senile changes, cerebral cortex	

in 2 patients. In three of the childhood cases the patients were mentally retarded; nine of the adult group showed mental disorders of one type or another.

As would be expected from the high incidence of extracerebellar signs, many parts of the central nervous system, apart from the cerebellum, were pathologically altered. In fact, in Case 3 of Schroeder and Kirschbaum,[150] and in the case of Titeca and van Bogaert,[155] the cerebellar cortical disease seemed to represent but a minor aspect of the pathological change. The cerebral cortex was involved in 5 cases (apart from those with banal senile changes); the basal ganglia and brain-stem structures, in 10 cases, and the spinal cord, in 3. The deep cerebellar nuclei were involved in 15 cases, and the olivary complex in 18.

It is of interest that the familial case reported by van Bogaert,[144] which was characterized by a long period of clinical stability and by cerebellar lesions of the restricted type, was also one of severe alcoholism complicated by cirrhosis of the liver; furthermore, at least two other members of this family, who were said to have had a similar cerebellar syndrome, also had severe alcoholism.

Group 5. *Cases characterized clinically by an onset in infancy and childhood and by mental retardation, and pathologically by a selective degeneration of the granule-cell layer* [102,149,164-167]

This group differs sharply from all the other types of cerebellar cortical degeneration in that the major pathological change consists of degeneration of the granule-cell layer, the other components of the cerebellar cortex being intact, or nearly so. Well-documented cases of this sort are extremely rare, and we have accepted only nine instances, four sporadic and five familial. Three of the four sporadic cases have been described by Ule[164]; in addition, he reportedly examined four other cases but no pathological description is provided, except for the statement that the changes were identical with those of his first case. Excluded from this group are Cases 2 and 3 of Vogt and Astwazaturow,[77] which are frequently cited as examples of granule-cell degeneration, but in which the primary

TABLE 8.—*Pathologically Verified Cases of Heredofamilial*

Author	Sex	Age of Onset, Yr.	Duration, Yr.	Mode of Evolution	Associated Conditions	Symptoms: Ataxia — Gait	Legs	Arms
Group A. Pathological Changes Restricted to or Predominant in the Anterior Superior Vermis and Hemispheres								
Holmes[109]	M	35	35	Slowly progressive	Hypogenitalism	+++	+++	++
Thorpe[110]	M	41	5	Progressive	Tuberculosis; epilepsy, schizophrenia (?)	++++	+++	++
Akelaitis[111] Case WI	M	42	2	Progressive		++++	++	++
Case Wa	M	50	1	Progressive	"Temperate" alc.; poor nutrition	++++	+++	+++
Weber and Greenfield[108]	F	60	18	Progressive		+++		
van Bogaert[103] Case 3	M	31	35	Progressive	Neurofibromatosis; small testes	+++		++
van Bogaert[104] Case 3 (Jean-Del)	M	58	5	Stable 1 yr.; progressive 4 yr.	Alcoholism; cirrhosis of liver	++++	+++	+++
Richter[105]	F	70	16	Progressive		++++	++++	++++
van Bogaert[106]	F	6	7	Progressive	Macular degen. "incontinentia pigmenti"; small ovaries; large thymus	++++	?	?

Cortical Cerebellar Degeneration in the Medical Literature

and Signs			Pathological Changes				
Dysarthria	Nystagmus	Others	Cerebellar Cortex	Deep Cerebellar Nuclei	Olives	Other Parts of CNS	Comment
++	+	Tremor, head	Severest, sup. vermis, flocculus, sup. hemispheres; less severe, inf. vermis; rest of hemispheres little affected or normal	0	+		1 sister, 2 brothers affected with cerebellar disease and endocrinopathy
++	0		Severest in sup. vermis, ant. lobes, simple lobules, ansiform lobules; inf. surface little affected	Dent. +	0	Chromatolysis Betz cells (? pellagra)	1, perhaps 2, brothers affected
+	0	Hypotonia, poor memory	Severe, sup. vermis; ant. lobes less affected; rest little or not affected	0	+	Diffuse loss nerve cells cerebral cort.	Maternal grandfather, mother, and 2 of 3 sibs affected
++	0	Hypotonia, confusion, incontinence	Severest, central lobule, (?) lingula; less, culmen; still less, ant. lobes, simple lobules	0	+	Loss nerve cells cerebral cort.; infarct. midbrain tegmentum	Brother of Case WI
+	0	Loss vision, hearing; emaciation	Severest, sup. vermis; hemispheres and inf. vermis much less affected; flocculi, vent. paraflocculi normal	0	+	Lacunar state basal gang., pons, red nucl.	Mother, 2 children affected
++	0	Kyphoscoliosis, myoclonus, rigidity, athetosis, memory loss	Sup. vermis and sup. parts hemispheres	Dent. + Roof +	0	Atrophy glob. pall., subthal. nucl.; gliosis, subst. nigra, thal. and capsule red nucleus	5 members of 3 generations affected; myoclonus, neurofibromatosis preceded cerebellar gait abnorms.; pigmentary deposits like Hallervorden-Spatz dis.
0	0	Ocular dysmetria, poor memory, chorea	Severe, sup. vermis, ant. lobes, simple lobules; less severe, crus I of ansiform lobules; slight, vent. vermis, dorsal paraflocculi, paramed. lobules	Dent. + Embol. + Glob. + Fastig. +	+	? Wernicke's dis.; atrophy, glob. pall., cerebral cort.; gliosis, optic paths	5 members affected in 3 generations; 2 others severe alcoholics
++	++	Dementia, hypotonia, absent A.J.'s, static tremor foot	Severest, sup. vermis, sup. hemispheres, with gradient laterally and posteriorly	Dent. + Fleece +	+	Atrophy, glob. pall.	15 affected members in 3 generations
++		Slight mental retardation	Generalized but predominant in "orodorsomedian" portion and dors. hemispheres	Dent. +	+	Degen. pyramidal tr., column Goll; atrophy post horns	2 sisters affected

TABLE 8.—Continued

Group B: Pathological Changes Diffuse and Approximately Equal Throughout Cerebellum								
Fraser[147]	M	2-3	31	Progressive		++		++
Crouzon and Bertrand[148] Mathieu and Bertrand[149] (Mme Querr)	F	28	36	Progressive 2 yr.; stable 34 yr.				++
Schroeder and Kirschbaum[150] Case 3	M	45	?10	Progressive	Pulmon. tbc.	++	++	++
Bielschowsky, Bouman and Sillevis Smitt[151]	M	27	27	Worse age 40	Seizures	+++		+
Richter[152]	M	47	18	Progressive		++++	+++	++
Hall, Noad, and Latham[153]	M	57	23	Progressive		++++	+++	+++
Hall, Noad, and Latham[154]	M	55	27	Progressive		++++	+++	++
Titeca and van Bogaert[155] Case "Fal"	M	44	6	Progressive	? Alcoholism; poor nutrition	++		
Carter and Sukavajana[156] Case 2	M	15	15	Progressive		+++	+++	+++
Case 3	F	14	4+	Progressive		++	++	++
Boder and Sedgwick[157,158]	F	1	9+	Progressive	Bronchiectasis, pulm. fibrosis; mucocutaneous telangiect.; dwarfism; abnorm. ovaries and thymus	+++	+++	+++
Malamud and Cohen[159]	M	1	6	Progressive	Seizures	++++	++++	++++

TABLE 8.—Continued

+		Unsteady eye movements, strabismus, pallor optic discs	Probably generalized				1 sister affected; only cerebellum and spinal cord studied microscopically
		Equinovarus, athetosis, rigidity, Parkinsonian tremor, bilat. extensor plantars	Generalized			Atrophy lumbosacral ant. horn cells, Deiters' nucl., column of Goll and spinocerebellar root V; senile changes cerebral cortex	1 sister affected
++		Psychic disorder, diplopia, aphasia, and apraxia	Generalized	Dent. + Embol. +	+	Slight degen. dors. spinocerebellar tr., sup. and inf. cerebellar ped.; nerve-cell loss diffuse cerebral cortex	Familial history dubious; changes in cerebellar cortex relatively slight
++	0	Disorientation	Generalized	Dent. fleece +	+	Neurofibrillary changes temp. and front. cort.; glial nodules striatum and pallidum	1 brother, 1 sister, youngest child, and perhaps father affected
+	+	Dementia	Generalized	Dent. +	0		1 brother, 1 sister affected
+++	+	Hypotonia, athetosis, dysphagia	Generalized	0	+	Senile changes cerebral cort.	7 members affected in 2, perhaps 3, generations
++	+		Severe throughout, most intense in declive and tuber	0	+	Senile changes cerebral cort.	Brother of preceding case
++		Hypotonia, hemichorea, cataracts, deafness, paranoia, confusion; CSF normal	Probably generalized	Dent. +	+	Atrophy glob. pall., subthal. nucl., putamen, subst. nig., sup. cerebellar ped.; gliosis mesencephalic nucl. V, cuneate, red nucl.	1 sister affected; changes in cerebellar cortex relatively mild; early case olivopontocerebellar atrophy
+++	0	Generalized rigidity, masked facies, dementia, bilat. pyramidal, extrapyramidal signs	Generalized	0	+	Degen. glob. pall., subst. nig.; mild degen. changes basis pontis; frontal cort. atrophy; brain wt. 755 gm.	Father and 6 of 19 sibs affected; cerebellum wt. 55 gm.
++	0	Generalized rigidity; masked facies	Generalized	Dent. +	+	Slight nerve-cell loss striatum, thal.; diffuse cerebral atrophy; brain wt. 780 gm.	Sister of preceding case, cerebellum wt. 60 gm.
+++	+	Adenoma sebaceum, dysphagia, aphonia; CSF normal	Generalized	Dent. + Dent. fleece +	0		1 sister affected; cerebellar changes probably not related to vasc. abnormality
		Tremor head, dementia, abducens weakness, spasticity followed by rigidity; CSF normal	Generalized	Dent. + Dent. fleece +	+	Atrophy red nucl., thal., glob. pall., subthal. nucl.; gliosis striatum, optic tr.; moderate atrophy vestib. nuclei	8 affected members in 2 generations, all males

TABLE 8.—Continued

Group C: Pathological Changes of Unusual Topography								
Hänel and Bielschowsky[110]	M	13	14	Progressive	Hypogenitalism			+
van Bogaert and Borremans[111] Case 3	M	?46	?11	Unknown		++		
Devos[105]	M	39	28	Progressive	Kyphoscoliosis	+++	+++	++
Biemond[101]								
Case TD	M	infancy	11	Progressive	Bronchiectasis; telangiectasia	++	++	++
Case LS	F	infancy	11	Progressive	Bronchiectasis; telangiectasia	++	++	++

process was probably Friedreich's disease. Also excluded is the granule-cell degeneration reported by Hunter and Russell,[51] which occurred in an adult and could be clearly related to poisoning by the inhalation of methyl mercury compounds.

Granule-cell degenerations have also been described in a wide variety of seemingly unrelated conditions, such as visceral carcinoma,[168,169] hypoglycemia and diabetic coma,[168,170] gangrene of the bowel and morphine intoxication,[171] and a large number of toxic and infectious states.[172] In these cases, the sole or principal criterion for the presence of granule-cell degeneration was a number of qualitative changes, such as *état glace*, pallor of staining, indistinctiveness of nuclear detail, and "conglutination." As has been pointed out, such qualitative changes, in the absence of a significant loss of cells, are probably artifactual or agonal in nature.

This is not to imply, however, that a significant granule-cell degeneration may not accompany certain other diseases of the nervous system. It is well known that some forms of cerebral lipoidoses are associated with a loss of granule cells.[89,90] Similar changes may be seen in cases of Jakob-Creutzfeld disease,[86] in the infantile diffuse cerebral degeneration of Alpers,[87,88] and, judging from our own experience, in some cases of anoxic encephalopathy occurring in infancy. All of these instances have been excluded from analysis because they represent diffuse disorders of the nervous system, of which the cerebellar affection is but a small, and relatively unimportant, part.

Only a few other points regarding the group of granule-cell degenerations require emphasis. In general, the clinical picture is indistinguishable from the commoner type of cerebellar degeneration occurring in infancy and childhood (Group 3). Particularly striking is the constant association with mental retardation. As with the other childhood cases, the hemispheres tended to be more involved than the vermis. The relative importance of hypoplasia in the production of the cerebellar disease is also not entirely clear in this group.

Group 6. *Miscellaneous cases*

Although a large number of cases reported in the medical literature could be readily classified in the manner indicated, there still remained 50 cases which defied the criteria set up for these categories, and

TABLE 8.—Continued

+		Mental retardation myoclonus	Diffuse, but hemispheres more affected than vermis; inf. vermis; more than sup. vermis	Dent. fleece + Dent. + Fastig. (?)	+	Slight status marmoratus	1 sister affected; patient died by suicide
		Dementia; lipomatosis, hypertension; CSF normal	Severe, central vermis and hemispheres, but changes elsewhere	Dent. fleece +	+	Lacunar state, loss cells in front. cort.; gliosis front. white matter; diffuse gliosis basal gang.; loss pigment subst. nigra	1 brother affected
++	+	Bilat. spasticity and clonus; ptosis; ocular dysmetria, gaze palsy, vertigo; CSF normal	Severe, dors. aspect of cerebellum; hemispheres more than vermis	Dent. fleece +	+	Atrophy of glob. pall., tegmental nucl.; pallor tr. of Helwig, pallor optic nerves	2 sisters and father affected
++		Hypotonia, then hypertonia and choreathetosis	Severe, pyramis, uvula, nodulus	0	0		Aplasia (?) 1 sister affected
++		Same as preceding case		0	0		Aplasia (?) 1 sister affected

which were therefore set apart in a miscellaneous group. Admittedly, the size of this group could be somewhat reduced if our criteria for classification were less rigid. Thus, the cases of Rossi,[174] Ohkuma, [182] Feizullaev and Sukhova,[206] and perhaps the case of Moyano [191] and Case 1 of Schroeder and Kirschbaum,[150] could be included in the alcoholic group (Group 1). Also, Case 4 of Brain, Daniel, and Greenfield [124]; Case 1 of Henson, Russell, and Wilkinson,[125] and one of Malamud's cases [127] probably belong with the carcinomatous groups (Group 2).

The question arises whether the cases in this miscellaneous group can be subdivided in a meaningful way. In view of the possible etiological role of malnutrition in some forms of cerebellar degeneration, it is of interest that, in addition to the alcoholic cases, there were five others (Murri [173]; Maas and Scherer, Case 1 [187]; Parker and Kernohan [189]; Birnbaum, Case 1 [197]; Ehrhardt [200]), and perhaps still another (Archambault [177]), in which a serious state of nutritional depletion immediately preceded the onset of the cerebellar disease.

Other associated factors of possible significance should be mentioned, in view of the attention that has been given them in the medical writings. Thus, an endocrine disorder of one type or another was a feature in four cases. A goiter was present in the case of Löwenberg,[190] and myxedema, in Case 1 of Henson, Russell, and Wilkinson [125]; atrophy of the thyroid and ovaries was found in the case of Ehrhardt,[200] and of the testes and anterior pituitary in Case 2 of Birnbaum.[197] A syphilitic infection was present in three patients: meningovascular syphilis in the case of Dimitri and Victoria [188]; asymptomatic syphilis in the case of Guillain, Bertrand, and Decourt,[181] and an old treated infection in the case of Smith, Gonda, and Malamud.[208] Tuberculomata of the brain were found in the case described by Guillain, Garçin, and Bertrand.[184] An episode of acute rheumatic fever just preceded the onset of the cerebellar disease in the case of Bertrand and Godet-Guillain.[199] There appears to be no logical reason to assign any special etiological significance to any of these factors.

At least 15 cases in this miscellaneous group were characterized pathologically by the presence of degenerative changes in many parts of the nervous system, in addition to those in the cerebellum. The parts

TABLE 9.—*Pathologically Verified Cases of Cortical*

Granule-Cell Degeneration: Cases Characterized Clinically by Onset in Infancy and Childhood and

Author	Sex	Age of Onset, Yr.	Duration, Yr.	Mode of Evolution	Associated Conditions	Symptoms: Ataxia, Gait	Ataxia, Legs	Ataxia, Arms
						A: SPORADIC CASES		
Scherer[103] Case FA 24/31		?	Less than 2 yr.		Idiocy			
Ule[104] Case 1	M	? Infancy	?15	No progression between ages 12-15	Ment. retard.	++		++
Case 6	M	Infancy	Less than 3	? Progressive	Mongolian idiocy; malnutrition	++		
Case 7	M	5-10	Less than 5	Progressive	Ment. retard.; seizures	+++		
						B: FAMILIAL		
Mathieu and Bertrand[148] Mme. Lec.	F	Infancy	About 40	Progressive		++	+	
Norman[105] Case 1	M	Infancy	18	Progressive	Ment. retard.	++++	+++	+++
Case 2	F	Infancy	44	? Nonprogressive	Ment. and phys. retardation	++		++
Jervis[106]	F	Infancy	?2	? Progressive	Ment. retard.	+++	++	++
Jervis[107]	F	Infancy	46	Stationary at least 20 yr.	Phys. and ment. retard.	+++		++

thus affected were the cerebral cortex, central cerebral white matter, striatum, globus pallidus, substantia nigra, and tegmental structures of the brain stem. The extracerebellar involvement was not consistent from case to case, so that the cases thus affected do not form a homogeneous group. Furthermore, cases with similar widespread degenerative changes were observed in conjunction with all types of cortical cerebellar degeneration, excepting the alcoholic one (Group 1). The presence of degenerative changes outside the cerebellum, therefore, does not serve to identify any particular type of cerebellar degeneration, although it tends to separate, even more sharply, the alcoholic variety.

A number of cases were not included in the miscellaneous group, and these require a word of explanation. Cases of cerebral cholesterosis and of leukodystrophy were not included, since the changes in the cerebellar cortex were most likely secondary to the destruction of axis cylinders in the white matter.[94-97] Also excluded is the case of van Bogaert and Colle,[210] since it possibly represents an instance of anoxic damage to the cerebellum; these authors

Cerebellar Degeneration in the Medical Literature

by Mental Retardation, and Pathologically by a Selective Degeneration of the Granule-Cell Layer

and Signs			Pathological Changes				
Dysarthria	Nystagmus	Others	Cerebellar Cortex	Deep Cerebellar Nuclei	Olives	Other Parts CNS	Comment
			Generalized				
++		Lumbar lordosis; dysmorphic cranium	Hemispheres severely affected; vermis and flocculi less	0	0	Loss of nerve cells, cerebral cortex	Author states that same description applies to his Cases 2-5
		Microcephaly; hypotonia; harsh heart murmur	Inf. hemispheres affected more than sup.; vermis better preserved	0			
++			Generalized, hemispheres more than vermis and flocculi	Dent. +	0	Old lesion R. front. lobe; (?) type	
	+	Generalized rigidity; bilat. ext. plantars; Parinaud's syndrome	Slight atrophy, especially sup. vermis		+	Atrophy sup. cerebellar ped., spinocerebellar tr., ant. lat. fasciculus	Mother and brother affected
++		Pendular K.J.'s	Generalized, least severe inf. vermis; preservation ext. granular layer	Dent. +	+	Gliosis, nucl. pontis, mid. cerebellar ped.; brain wt. 850 gm.	2 sibs similarly affected; 1 sib deaf, 1 sib. seizures; patient died of tbc enteritis
++			Generalized; nodulus nearly normal	Dent. +	0	Brain wt. 928 gm.	1 sib. affected; patient died of tbc meningitis
	+	Hypotonia	Hemispheres severer than vermis and flocculi	Dent. fleece +	+		2 sibs affected
++	0	CSF normal	Hemispheres more than vermis	0	+	Brain wt. 980 gm.; poorly developed gyral pattern; diffuse loss nerve cells in cerebral cort.	Identical twin affected; mother "somewhat dull"

described a patient who suffered from severe, recurrent seizures and who developed a cerebellar syndrome in the last year of his life.

F. Spontaneously Occurring Cortical Cerebellar Degeneration in Animals

A variety of animal species may be affected by a spontaneously occurring degenerative disease affecting the cerebellar cortex predominantly and in a diffuse manner. Included in this category are the "shaker" fowl,[211] the "jittery" chick,[212] the "agitans" mouse,[213] the "daft" lambs and other cerebellar defects of this species,[214] cats,[215] and calves.[216] In the litter of kittens described by Herringham and Andrewes,[217] the Purkinje cells were spared, and the granule cells were severely affected. Innes, Russell, and Wilsdon[218] have described a form of cerebellar degeneration in Hereford calves, which they considered to be superimposed on a hypoplasia of that organ. A similar type of cerebellar lesion has been observed in Airedale dogs.[219] Although all of these forms of cerebellar degeneration in animals are genetically determined, no single mode of inheritance seems operative.

TABLE 10.—*Miscellaneous Pathologically Verified Cases of*

Author	Sex	Age of Onset, Yr.	Duration, Yr.	Mode of Evolution	Associated Conditions	Symptoms: Ataxia: Gait	Ataxia: Legs	Ataxia: Arms
Murri[178]	F	59	½	Rapid evolution; stable 7 wk.	Enteritis with weight loss, malnutrition	++++		++
Rossi[174]	M	59	9	Progressive 3 yr.; stable 4 yr.; progressive 2 yr.	Cirrhosis of liver, ascites; onset after 6 wk. diarrhea	+++	+++	+
Anglade and Jacquin[176]	F	75½	?	?	Chronic psychosis and otitis	+++		
Léjonne and Lhermitte[176]	F	63			Weber's syndrome			
Archambault[177]	M	17	48	Stable 23 yr.; slowly progressive 25 yr.	Onset after severe febrile gastrointest. disease	+++	+++	+++
Jelgersma[176]	M	75	13	Slowly progressive 8 yr.; stable 5 yr.		++++	++++	++++
Marie, Foix, and Alajouanine[167] Case 1		68	14	Slowly progressive		++++	+++	+
Case 3	M	60				+++	+++	+
Schroeder and Kirschbaum[166] Case 1	M	30	22	Progressive	Moderate alc.	+++	+++	++
Case 2	F	47	⅔	Progressive		+		

Cortical Cerebellar Degeneration in the Medical Literature

and Signs			Pathological Changes				
Dysarthria	Nystagmus	Others	Cerebellar Cortex	Deep Cerebellar Nuclei	Olives	Other Parts CNS	Comment
++	+	Vertigo, diplopia, postural tremor, loss of memory, emaciation	Generalized	0	0	Chromatolysis cranial nerve nucl.; pyramidal cells cerebral cort., cells of ant. and post. horns of cord	Clinical and pathological features of pellagra
++	0	Hyperreflexia; ext. plantars; hypalgesia legs	Severest culmen, declive, ant. lobes, and flocculi; less severe, paramedian lobules, cent. lobule, lingula, pyramis, dors. paraflocc.; rest normal	0	0		
	0		Generalized			Cerebral hemisphere, 1,030 gm.; cerebellum and brain stem 90 gm.; meningeal thickening	No microscopic examination of brain except cerebellum
		Abnormal mental state	Generalized	Dent. + Fastig. +	+	Old infarct, pons and midbrain; atrophy, sup. and inf. cerebellar peduncles	So-called "olive-rubro-cerebellar atrophy"
+		Ocular dysmetria	Severe sup. vermis, ant. lobes, simple lobules, dors. paraflocc.; less, ansiform, paramed. lobules, flocculi, uvula, nodulus; mild, vent. paraflocculi and pyramis	Dent. fleece + Fastig. fleece +	0	Slight pallor column Goll, dorsal spinocerebellar tr.	
++++		Hypotonia	Generalized	0	0		
±	+	Hypotonia	Sup. vermis most affected; inf. vermis, ant. lobes somewhat less; least in inf. hemispheres; vent. paraflocc. normal	Fastig. fleece +	+	Pallor column Goll, pyramidal tr.	
+++	0		Same as Case 1	Fastig. fleece +	+		
++	0	Progressive dementia, increased tone	Generalized	Dent. + Embol. + Glob. + Fastig. +	+	Neuronal loss, gliosis cerebral cort., especially temp. and parieto-occip.; loss large nerve cells striatum; shrinkage glob. pall.	Perivasc. lymph. infiltra. near deep cerebellar nuclei
++		Immobile facies, catelepsy, disorientation	No topographical information	Dent. + Embol. + Glob. + Fastig. +	+	Focal loss nerve cells, cerebral cort.	

TABLE 10.—Continued

van Bogaert[179]	M	50	6	Progressive		+++	+++	+++
Guillain and Bertrand[180]	M	44	43	Progressive		++	++	++
Guillain, Bertrand, and Decourt[181]	M	69	8	Slowly progressive 2 yr.; stable 3 yr.	Asymp. neuro. syphilis	++++	+++	+
Ohkuma[182] Case 1	F	?66	?1/6	Progressive	Alc.; cirrhosis liver			
Case 2	F	?47			Severe alc.	++	++	++
Case 3	F	?46			Severe alc. cirrhosis liver			
Case 4	M	?52			Severe alc.	+++		
Lüthy[183]	F				Senile dement.			
Guillain, Garcin, and Bertrand[184]	M	70	3	Progressive 1 yr.; stable 2 yr.		++++	+++	+
Kirschbaum and Eichholtz[185]	M	20	31	Slowly progressive	Rheumatic fever (?) after onset of cerebellar disease	+++	+++	+++
van Bogaert and Bertrand[186]	F	38	20	Progressive		++++	++++	++++
Maas and Scherer[187] Case 1	F	30	4	Progressive	Onset after severe bout of vomiting	+++	+++	+++
Case 3	M	34	39	Stable many yr.	(?) 3 strokes	+++	±	±
Dimitri and Victoria[188]	M	50	1	Progressive	Syphilis	++++	+++	++
Parker and Kernohan[189]	M	48	1	Progressive	Severe weight loss at onset; peptic ulcer; "membranous typhlitis"	+++	+	++

TABLE 10.—Continued

+++	0	Memory loss and confab.; disorient.; dysphasia; catelepsy	Hemispheres more affected than vermis	Dent. +	±	Loss nerve cells cerebral cort., esp. front., parietal	
++		Severe dementia	Vermis, ant. lobes, simple lobules		+	Diffuse "necrotic nodules" cerebral cort., basal gang., pons; degen. corticospinal tract	
	+		Generalized; severest sup. aspect; most intense culmen	0	+	Lacunae in pons, basal ganglia	
+	0	Delirious, amnestic state	Insufficient topographical information		0	Loss nerve cells cerebral cort., striatum, pallidum; Wernicke's dis.	
	+	Areflexia, loss pos. sense; Korsakoff's psychosis	Same as Case 1			Frontal convolutional atrophy; Wernicke's enceph.	Father, brother, husband also severe alcoholics
+		Polyneuropathy	Same as Case 1			Wernicke's dis.	
+	0	Areflexia legs; D.T.'s	Generalized			Loss nerve cells in cerebral cort. striatum; Wernicke's dis., polyneuropathy	
			Severe sup. vermis, paravermian portions ant. lobes, simple and ansiform lobules; inf. surface less affected or normal				Cerebellar disease discovered post mortem, age 79
0	0	Generalized rigidity preceding cerebellar signs; hypotonia	Generalized	0	0	Tuberculomata in meninges and in one dentate nu.	
+	0	Scant bodily hair	Severe culmen, declive, ant. lobes, simple lobules, flocculi; rest of vermis less affected; rest little or normal	Dent. + Embol. + Glob. +	+	Diffuse atheroscler. infarct. cerebrum, subst. nig., red nuclei	Strong family history of alcoholism
++		Equinovarus; rigidity limbs	Severe, declive, ant. lobes, simple lobules; less, ansiform lobules, dors. paraflocc.; rest, normal	Dent. + Dent. fleece +	+	Endarteritis in vicinity of olivary and dentate nucl.; atrophy cerebral peduncles	
++	?	Hypotonia; weakness, lateral gaze	Generalized	Dent. fleece +	+	Focal demyelination post. lat. columns	Perivasc. inflammatory cells
++	+	Slight dement.	Sup. vermis, flocculi and probably paravermian portions ant. lobes, simple lobules	Dent. fleece +	+	Recent infarcts, cerebrum	
++		Vertigo	Generalized, severer in vermis (?)	Dent. +	+	Meningovascular syphilis; mild degen. transv. fibers of pons, mid. cerebellar ped.	
+	+	Diplopia, generalized atony; CSF normal	Diffuse, severer in hemispheres than vermis	Dent. +	0		Meningeal and perivasc. inflammatory cells

TABLE 10.—*Miscellaneous Pathologically Verified Cases of*

Author	Sex	Age of Onset, Yr.	Duration, Yr.	Mode of Evolution	Associated Conditions	Symptoms: Ataxia — Gait	Ataxia — Legs	Ataxia — Arms
Löwenberg[100]	F	?46	?4		Goiter			
Moyano[101]	F	49	12	Slowly progressive	Alcoholism	++++	+++	++
Moyano[101]	F				Senile dement.			
Tretyakov and Oleynikova[102]	M	23	1	Progressive several mo., then stable	Malaria; ment. retardation	++++	++++	+++
Courville and Friedman[104]	F	?33	?9	(?) Progressive	Meningitis in infancy; chorea since childhood; ? skull fracture childhood; Ca stomach late	+++	++	++
Garcin, Bertrand, and Godet-Guillain[105]	M	late 60's	2+	Stable at least 18 mo.	Ca stomach, late	+++	+++	+++
Hemphill and Stengel[106]	F	?41	?18					
Birnbaum[107] Case 1	M	52	8	Progressive	Scurvy at onset of cerebellar disease	+++	+++	++
Case 2	M	16	14	Progressive	Hypogenitalism and infantilism; nodular goiter	++++	+++	+++
Guillain, Bertrand, and Godet-Guillain[108]	F	17	24	Progressive		++++	+++	+++
Bertrand and Godet-Guillain[109]	F	33	22	Progressive 14 yr.; stable 8 yr.	Acute rheumatic fever 1 mo. before onset of cerebellar syndrome; Ca ovary late	+++	+++	+++
Ehrhardt[110]	F	50	3		Severe weight loss beginning 3 mo. before onset cerebellar disease	++++		
Dimitri and Aranovich[201] Case 2	M	60	2½	Progressive		++++	+++	+++

and Signs			Pathological Changes				
Dysarthria	Nystagmus	Others	Cerebellar Cortex	Deep Cerebellar Nuclei	Olives	Other Parts CNS	Comment
		Dementia	Degen. vermis, ant. lobes, simple lobules, portion ansiform lob.	0		Pick's disease	
++		Rigidity of legs	Generalized		0	Cerebral convol. atrophy	
			Severe lingula, central lobule, culmen, less declive; minimal rest of cerebellum	0	0	Diffuse cerebral cort. atrophy	Cerebellar disease found post mortem, age 78
++	0	Catalepsy; dysplastic skull	Patchy but diffuse	Dent. (?)	+	Atrophy sup. midcerebellar ped.; partial degen. subst. nig.; brain wt. 800 gm.	
++	0	Pendular K.J.'s	Superior vermis and adjacent parts hemispheres; meningocerebellar scarring	0	0		
±	0	Hypotonia	Severe sup. vermis; less. ant. lobes, simple lobules; minimal involvement, flocc.; rest normal	Dent. +	+		
		Dementia	Generalized	?	+	Brain wt. 870 gm.; senile changes cerebral cort., basal ganglia	Authors describe argentophilic plaques in cerebellar cortex
++		Progressive dementia and chorea; rigidity legs	Severe ant. sup. vermis and hemispheres; rest minimal	Dent. fleece + Dent. +	+	Loss small nerve cells and gliosis striatum; degen. sup. oliv. nucl.; nerve-cell loss cerebral cort.	
++	0	Hypotonia; dement.; chorea	Generalized	Dent. fleece +	+	Atrophy striatum; severe cell loss in cerebral cortex	Atrophy testes, ant. lobe pituitary
+++	++	Loss vison; hypotonia; later rigid., decerebrate postures, dement., chorea, myoclonus, bilat. ext. plantars	Severe, culmen, declive, ant. lobes, simple lobules, flocculi; less severe, ansiform lobules; minimal, vent. paraflocculi	0	+	Pallor spinocerebellar tr.; diffuse loss cortical nerve cells	
++	0	Vertigo, hypotonia; CSF normal	Generalized	Dent. +	+	Degen. nucl. basis pontis	
		CSF normal	Generalized	Dent. fleece +	0		Atrophy thyroid, ovaries
++		Tremor head, dement.	Sup. surface hemispheres	Dent. +	+	Mild degen., red nucl. thal.; perivasc. necrosis, cerebral white matter; atrophy, corpus callosum, corticospinal tr.; nerve-cell loss cerebral cort.; widespread vasc. dis.	

TABLE 10.—Continued

Buchanan, Overholt, and Neubuerger[101]	F	30	15	Progressive	Ca lung, late	+++	+++	+
Munch-Petersen[103]	F	45	1½	Progressive	Progressive	++++	+++	++
Simma[104]	M	40	4	Progressive		++	+	++
Brain, Daniel, & Greenfield[104] Case 2	M	48	½	Progressive		+++	+++	++
Case 4	M	56	½	Progressive	Ca lung	+++	+	+
Henson, Russell and Wilkinson[105] Case 1	F	59	1¼	Progressive	Ca breast; myxedema	++	+++	
Verhaart[106]	F	39	11	Progressive				+++
Feizullaev and Sukhova[106] Case 3	M	29	?	Abrupt	Severe alc.; nephrosis; generalized amyloidosis	+++	+++	+++
Krebs and Plantey[107]	M	59	12	Progressive		+++		
Smith, Gonda, and Malmud[108]	M	58	8	Progressive	Syphilis, age 26, moderate alc.	++++	+++	+
Hills and Mancall[109]	M	67	5	Progressive		++	+	+
Malamud[197]	M	66	½	Progressive	Bronchogenic carcinoma	+++	+++	+++

TABLE 10.—Continued

+++	++	Vertigo, dement. late	Severe sup. vermis, sup. hemispheres	Dent. +	+	Pick's disease; metastatic tumors brain	Family history (?)
++	++	Vertigo, hypotonia, areflexia, dement.	Generalized	Dent. fleece +	0	Degen. sup. and to less extent mid. cerebellar ped.	
	++	Dement., front. lobe signs, spasticity, catatonia; CSF prot. 84 mg. %; 1st zone coll. gold curve	Generalized		0	"Late life leukodystrophy" front. white matter	
++		Diplopia, vertigo, tinnitus, dement., hypotonia, ophthalmoplegia, ptosis	Vermis much more than hemispheres	0	0		
	++	Vertigo, diplopia, hypotonia; CSF: 22 lymphs, 80 mg. % prot.	No topographical information	0	0	Degen. direct spinocerebellar tr.; early changes post. columns, increased glia, supraoptic nuclei	Perivascular and meningeal lymphocytes
++	++	Diplopia, paresthesias, hypotonia, resting tremor, mild dement., later paralyzed legs and bilat. ext. plantars; CSF: 20 lymphs, prot. 90 mg. %, coll. gold 223321	No topographical information	Dent. +		Degen. subthal. nucl., strio-Luysial fibers, sup. cerebellar ped.	Perivasc. inflamm. cells and neuronophagia brain stem and sup. cerebellar ped.; involvement cerebellar cortex relatively mild
++	+	Diplopia, hypalgesia feet and hands, hemifacial myoclonus, hypotonia; later paralysis., dement., forced crying and laughing	Generalized	Dent. + Roof +	+	Infarcts, mesencephalon and dienceph.; mild degen. Gowers' tr.	
++	++		No topographical information	0		Swelling, chromatolysis pyramidal cells	Cortical changes of pellagra
		Myoclonus, later cerebellar syndrome	Generalized; severe, in vermis	Embol. + Glob. + Fastig. +	0	Lafora-like inclusions tegmentum, mesenceph., and pons	
++	0	Choreoathetosis, hypotonia, catalepsy, pseudobulbar palsy, dement.; CSF normal	Generalized	Dent. + Dent. fleece +	0	Degen. sup. cerebellar ped., red nucl., subthal. nucl., glob. pall., thal., subst. nigra	Involvement of cerebellar cortex relatively mild
++		Cerebellar syndrome, then Parkinsonian symptoms, dement., front. lobe signs, seizures	Severe ant. sup. vermis and hemispheres	Dent. fleece + Embol. + Glob. + Fastig. + Dent. +	+	Degen. sup. cerebellar ped., subst. nig., glob. pall., striatum cerebral cortex	Involvement of cerebellar cortex relatively mild
+++		Nausea, vomiting, diplopia, vertigo	No topographical information	Dent. +		Normal	Probably carcinomatous degeneration; proliferation of microglia and astrocytes in dentate nucl.

Such animal disorders may conceivably shed some light on the familial, childhood, and granule-cell degeneration of the cerebellum; they seem to have no immediate relationship to the sporadically occurring forms in adults.

G. Restricted Cerebellar Cortical Degeneration in the Alcoholic Patient: A Clinical-Pathological Entity

It is appropriate at this juncture to consider the status of the restricted cerebellar cortical degeneration in the alcoholic patient as a nosological entity. From the clinical point of view, the striking stereotypy of the syndrome is particularly significant. The homogeneity of the clinical manifestations, as we have observed them in 50 patients, has been fully described. Attention has also been drawn to the clinical parallelism between our cases and the 11 pathologically verified instances of cerebellar degeneration in alcoholic patients, drawn from the literature (Group 1). Furthermore, this cerebellar syndrome is probably identical with the one described by several other authors. There are now a number of purely clinical reports in the medical literature dealing with this type of cerebellar disease in alcoholic patients. Five such cases have been described by Romano, Michael, and Merritt[220]; two, by Uzman[3]; six, by Skillicorn[221]; six, by Alajouanine and others,[222] and at least sixteen, by Chodoff, Auth, and Toupin.[223] Probably the 2 cases reported by Pauly, Bergouignan, and Verger[224] and the 10 cases of Decker, Wells, and McDowell[225] should also be included. If one adds to this number our own clinical cases, and the pathologically verified cases, both our own and those in the literature, then there are about 110 recorded cases, an indication that this condition is far from rare. In fact, in our experience, the alcoholic variety has proved to be by far the commonest form of chronic cerebellar disease. However, this may merely indicate the extremely high rate of alcoholism in the Boston population.

Just as the clinical findings are stereotyped, so, too, are the pathological ones, as has repeatedly been stressed. Judging from our experience, many more such cases would be uncovered if the cerebellum were cut in the sagittal plane.

Although these clinical and pathological features are highly characteristic, we do not wish to imply that they are specific to the alcoholic variety of cerebellar disease. In some of the familial cases (Holmes' type) and in some of the sporadic, nonalcoholic ones, the same general topography of lesions was present. Nevertheless, considering the frequency with which this syndrome has been encountered on a background of alcoholism, and the stereotypy of the pathological and clinical picture, particularly in regard to the long periods of stability, it is our feeling that the restricted form of cortical cerebellar degeneration, seen in the serious alcoholic, represents a clinical-pathological entity.

It should be mentioned that other types of cerebellar disease have been described in the alcoholic patient, but in these instances the relationship is seemingly a purely coincidental one. This appears to be the case in the patients with olivopontocerebellar atrophy recorded by Schultze[226] and by Fickler.[227] One of us (R. D. A.) has encountered two instances of focal panatrophy of the cerebellum in alcoholic patients; the small numbers of these cases would suggest that here, also, no mechanism other than coincidence was operative. The curious case of Vidal and Bonhour,[228] allegedly one of cerebellar atrophy in an alcoholic patient, was so complicated by trauma that the role of alcohol cannot properly be assessed.

Clinically, the syndrome with which we have been dealing must not be confused with the transient variety which occurs in alcoholic patients after a severe drinking bout. The latter syndrome has been well described by Bechterew,[229,230] by Ohmari,[231] and Dosožkov, Kočka, and Uhl[232]; and we have been able to verify its occurrence

in our own patients. It is characterized by the presence of cerebellar signs which last usually for several days or weeks, occasionally longer, but which always improve. Its pathological basis has never been established.

The relationship between the cerebellar degeneration under discussion and Wernicke's disease may also be suitably considered at this point. In our clinical experience, an ataxia of stance and gait is a prominent feature of Wernicke's disease, although the patients show little or no impairment of the individual movements of the legs.[233] This ataxia, which may be very gross in the acute stages of the illness, always improves with the passage of time, but does not disappear entirely in a small proportion of patients. It will be recalled that 4 of our 11 pathologically verified cases of cerebellar degeneration also showed the characteristic lesions of Wernicke's encephalopathy. This would suggest that the ataxia of Wernicke's disease, at least in its severe and persistent form, has its basis in a lesion of the superior portion of the cerebellar cortex, particularly the vermis. The transient form of the ataxia would be explained by the fact that the lesion was either reversible or so subtle that it could not be detected pathologically.

Finally, a few remarks should be made regarding the title which we have applied to the cerebellar disease under discussion, i.e., "restricted degeneration of the cerebellar cortex in alcoholic patients." The terms "restricted" and "cortical" seem entirely logical, in view of all that has been said. We have avoided the terms "atrophy" and "abiotrophy," since these often carry a specific connotation in regard both to the tempo of evolution of a disease process and to the etiology in terms of diminished neuronal vitality or viability. We would therefore agree with Greenfield[234] that the noncommittal term "degeneration" is preferable for these disease processes. The qualification "in alcoholic patients" is cumbersome but, nevertheless, more accurate than the term "alcoholic cerebellar degeneration." The latter term implies that alcohol itself is the etiological agent, and this conclusion is probably unjustified, as has been pointed out. Finally, we do not regard the adjective *tardive* of Marie, Foix, and Alajouanine[107] to be particularly applicable, since an average age of onset of under 50 years can hardly be considered "late life."

Summary and Conclusions

Clinical observations have been made on a group of 50 alcoholic patients (46 men and 4 women), all of whom were afflicted with a remarkably uniform cerebellar syndrome. The most prominent abnormality was an ataxia of stance, and gait, as well of the individual movements of the legs. The arms were relatively little affected, and nystagmus and dysarthria were absent in the majority of cases. Instability of the trunk was a common finding, but an independent tremor of the head was rare. Hypotonia was observed in 14 patients and an unusual postural tremor in 6.

In regard to the natural history of the illness, the patients could be divided into three categories. In the first group, which comprised half the patients, the disease evolved over a period of several weeks or months, after which it remained unchanged for many years. In the second group the disease evolved over a period of several years, but in some of these, also, the clinical condition eventually stabilized. In the third, and smallest, group, mild stationary signs of cerebellar disease had been present for several years; on this background there occurred a worsening of the cerebellar signs, and these, in turn, again stabilized.

The essential pathological change, as observed in 11 autopsied cases, was a degeneration of all the neurocellular elements of the cerebellar cortex, particularly of the Purkinje cells, the changes being strikingly restricted to the anterior and superior aspects of the vermis and the hemispheres. The olivary nuclei were almost always in-

volved; the fastigial, globose, emboliform, and vestibular nuclei were less consistently affected. The dentate nuclei, cerebellar white matter and peduncles, the spinocerebellar tracts, and other brain-stem nuclei were essentially unaltered.

The pathological alterations, especially in the mildly affected cases, were best displayed by sectioning the cerebellum in the sagittal plane, the initial cut being made in the midline through the vermis.

Apart from the changes in the cerebellum and its immediate connections, lesions characteristic of polyneuropathy were present in five cases, of hepatic encephalopathy in five cases, and of Wernicke's disease in four cases.

An attempt was made to quantitate the pathological changes by determining the number of Purkinje cells per unit length of cerebellar cortex, and comparing the numbers obtained in the patient material with the numbers in control subjects, both alcoholic and nonalcoholic, without cerebellar disease (Table 4). The quantitative data obtained in this way supported the findings obtained by customary methods. There was a reduction in the number of Purkinje cells in three of four control subjects past the age of 70, but it was mild in degree, and never as severe as in any of the pathological cases.

The pathological changes were either entirely confined to that portion of the cerebellum which lies anterior to the primary fissure, i.e., the anterior lobe of Larsell, or else the bulk of the lesion was located in this territory. In this respect, the characteristic clinical state could be regarded as an "anterior lobe syndrome." Nevertheless, the lesion did not conform precisely to this territory, or to what has been designated as the "paleocerebellum," or to any of the other divisions based on comparative morphology.

The relation between the clinical and the pathological findings in our cases is particularly meaningful in the light of recent concepts concerning somatotopic localization in the cerebellum. The parts consistently involved in the pathological process, namely, the central lobule and the anterior folia of the anterior lobe, correspond to the "leg area" in the experimental animal; this is in keeping with the fact that an ataxia of gait and incoordination of the legs were the most prominent clinical features in all our cases. Although the culmen was also frequently affected, the lateral extensions into the most posterior folia of the anterior lobe was spared; thus much of the experimentally demonstrated "arm area" was uninvolved, and, indeed, the arms were only slightly affected in our patients. The bulk of the region considered representative of the head and neck (i.e., the declive and simple lobules) was spared, and, correspondingly, there were no clinical signs referable to this zone except for an inconstant and minimal dysarthria.

In regard to etiology, many factors were considered, but only two seemed of importance—alcohol and malnutrition. Although the abuse of alcohol was a feature common to all our patients, six patients had actually been abstinent for varying periods of time before the onset of their cerebellar disease. It is difficult under such circumstances to accept the toxic effects of alcohol as the direct causative agent. Evidence gleaned from the history and examination indicated that fully three-quarters of the patients suffered from undernutrition when they were first seen by us. Malnutrition may also have been a factor in the remaining patients, who came to our attention only years after the onset of their illness, after a period of abstinence and concomitant improvement in their eating habits.

An extensive review of the medical literature has disclosed 120 pathologically verified cases of cerebellar degeneration in which the disease process was limited to, or predominant in, the cerebellar cortex. From this group it has been possible to derive a number of subdivisions, each with distinctive clinical and pathological features (Tables 5-10).

(*a*) Sporadic cases beginning in adult life, on a backgorund of prolonged alcoholism, characterized clinically by a chronic course, usually with long periods of stability, and pathologically by predominance of the degenerative changes in the anterior superior vermis and hemispheres

(*b*) Sporadic cases occurring in adult life, associated with carcinoma, characterized clinically by a subacute, steadily progressive course, and pathologically by diffuse and approximately equal degenerative changes in all portions of the cerebellar cortex

(*c*) Sporadic cases beginning in infancy and childhood, usually progressive and associated with mental retardation, characterized pathologically by diffuse changes in the cerebellar cortex, generally of greater severity in the hemispheres, and by lesions in other parts of the central nervous system

(*d*) Heredofamilial cases of cortical cerebellar degeneration

(*e*) Cases characterized pathologically by a selective degeneration of the granule-cell layer, and clinically by an onset in infancy of childhood and by mental retardation

(*f*) Miscellaneous cases

Considering the frequency with which this syndrome has been encountered on a background of alcoholism, and the stereotypy of the pathological and clinical picture, particularly in regard to the long periods of stability, it is our feeling that the restricted form of cortical cerebellar degeneration seen in the serious alcoholic represents a clinical-pathological entity.

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Modification of Alpha-Wave Responsiveness to Light by Juxtaposition of Auditory Stimuli

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From the earliest studies of the human electroencephalogram, the disappearance ("blocking") of the alpha activity upon presentation of a visual stimulus has been regarded as among the most consistent of the electrical responses of the brain to external stimulation. While the effect of light upon the electroencephalogram has varied considerably in degree from one subject to another, the response in a single subject in the waking state has generally been considered to be a consistent one, i. e., a response which does not habituate. The predictability of this response has led to its being employed as the unconditional stimulus in numerous experiments on the development of conditioned cerebral responses.

While studying the development of conditional cerebral responses in man, it has been observed both by me and by others,[1] that repeated presentation of paired sound and light stimuli in the same temporal relationship leads to the attenuation of the expected alpha response following the appearance of light. This loss of responsiveness to visual stimulation has previously been ascribed to habituation. The following studies were undertaken to determine whether this diminished responsiveness to visual stimulation could indeed be explained by an habituation mechanism or whether other mechanisms might be involved in this change.

Methods

Studies were carried out on 14 normal subjects, predominantly medical students and laboratory personnel, without known disease of the nervous system. The subjects were seated comfortably in a quiet and semidarkened room facing the light source with the eyes closed. Recordings of the brain waves were made with a Grass Model III-D electroencephalograph. Bipolar recordings were made utilizing needle scalp electrodes placed in frontal, temporal, and occipital or frontal, parietal, and occipital areas bilaterally. The auditory stimulus was produced by a Beltone Audiometer delivering through earphones a sound to one ear of 500-cps frequency at approximately 40-45 db. above the level of audibility. A masking noise was utilized on the opposite ear to block out extraneous noises. Light stimulation was provided by a 150-watt frosted bulb with white reflector placed approximately 12 in. from the subject's face. Diligent efforts were made to keep the subject alert throughout the entire testing periods.

Studies were performed during two testing periods. During one period the subject was presented first with a light stimulus of three seconds' duration, repeated several times to ascertain that light provoked the expected suppression of alpha activity. This was followed by repetitive sound stimuli, each of four seconds' duration. The tone presentations were irregularly spaced, averaging approximately one stimulus every 10 seconds until at least five successive tone presentations failed to produce any noticeable suppression of the alpha activity. Paired sound and light stimuli were then delivered to the subject, the sound appearing 0.8-1.0 second before the light, with the two continuing simultaneously for three seconds before cessation. The interval between the onset of the sound and the appearance of the light was timed automatically and remained constant in each subject. The paired stimuli were presented 60 or more times at irregular time intervals, averaging once every 10-15 seconds, in order to avoid cyclic conditioning and to attempt presentation of the stimuli when alpha activity was most prominent.

During the other test period, usually several days following the one described above, and under similar test conditions, the subject was presented repeatedly with light stimuli of three seconds' duration, the light appearing 50 times for periods of

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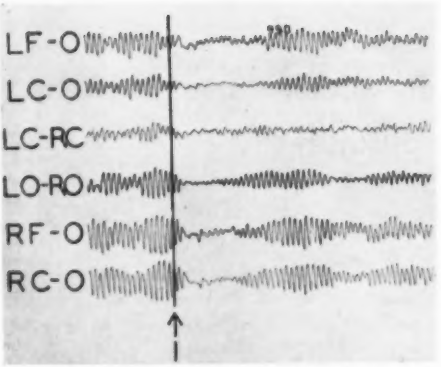


Fig. 1.—Usual suppression of alpha rhythm following appearance of light, whose onset is indicated by the arrow.

three seconds each at random intervals, averaging once every 10 seconds.

The records were then evaluated for the effectiveness of the visual stimulus in causing suppression of the alpha activity in the two series of tests. The effect of each visual stimulus was evaluated as to whether or not it was followed by blocking of the alpha activity, and, if so, the duration of the disappearance of alpha activity was measured, the length of time from the appearance of the light to the reappearance of alpha activity being the measurement used.

In the series employing sound-light combinations, when a conditioned cerebral response (temporary cerebral connection) appeared, manifested by the obliteration or striking depression of the alpha rhythm following the presentation of the tone and before the appearance of light, this observation was not included in the results, since the response to the light per se here obviously could not be ascertained. Since 60 or more sound-light combinations were presented to each subject, there usually remained 50 sound-light combinations manifesting no conditioned response which could be compared with the 50 presentations of light alone.

The number of times the light was followed by blocking of the alpha rhythm and the duration of its suppression were then grouped for each subject into totals for each group of 10 successive presentations in the series (i. e., 1st to 10th presentations, 11th to 20th presentations, etc.). The average number of times that light provoked disappearance of alpha activity and the average duration of each disappearance were then determined for the entire group of 14 subjects and the findings for the two series of observations compared.

Observations

Figure 1 illustrates the usual disappearance of alpha activity following the presentation of a visual stimulus alone. Figure 2 shows the initial response to combined sound and light stimulation (after the patient has been habituated to the auditory stimulus alone), when the tone causes no change in alpha activity but when light is promptly followed by obliteration of the alpha rhythm. Figure 3 illustrated the development of a conditioned cerebral response, the tone causing disappearance of the alpha activity before the appearance of the visual stimulus. Figures 4, 5, and 6 are examples of the observations frequently made after repeated stimulation, with tone-light combinations showing the lack of response of the alpha activity to either the sound or the light stimulus.

Table 1 indicates the average number of times light provoked blocking of alpha ac-

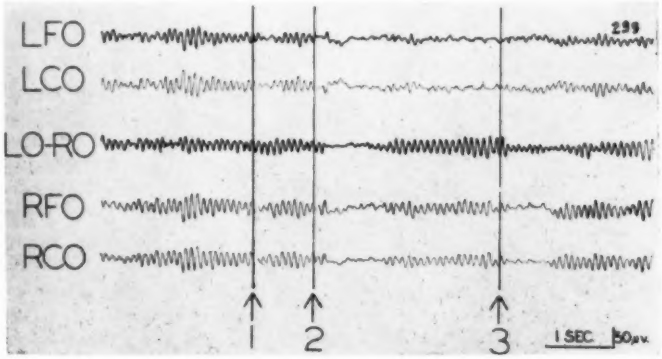


Fig. 2.—Usual suppression of alpha rhythm following the appearance of light after habituation to sound. In this Figure and in Figures 3 to 6, arrow *1* indicates the onset of sound stimulus; arrow *2*, the appearance of light, and arrow *3*, their simultaneous disappearance.

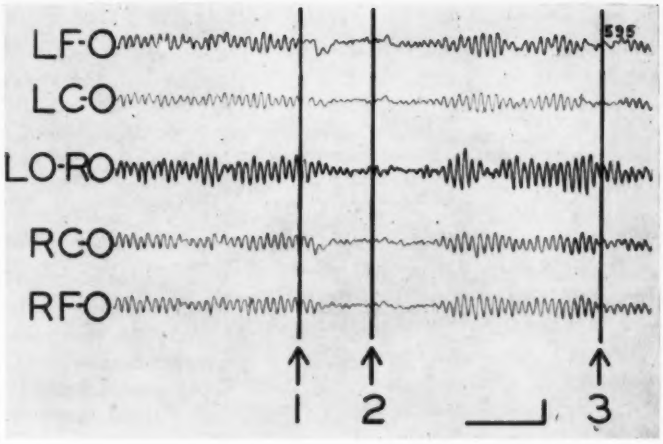
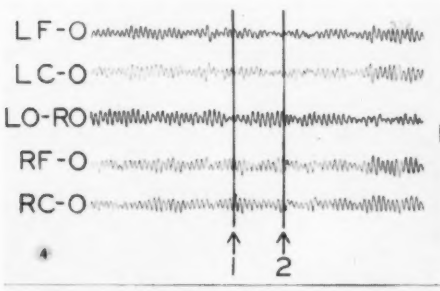
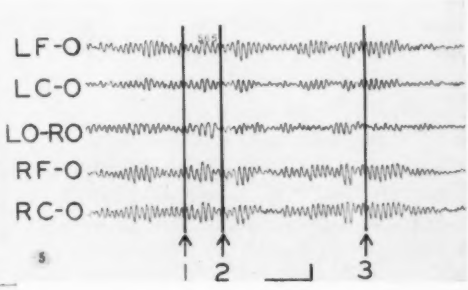
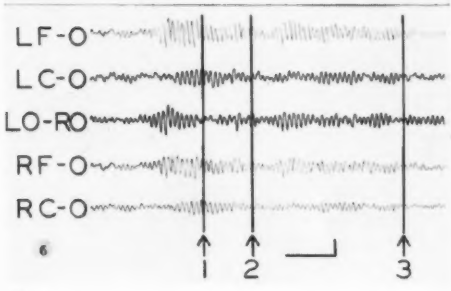


Fig. 3.—Demonstration of conditioned cerebral response (temporary cerebral connection) showing blocking of alpha activity following onset of sound before the appearance of light. For interpretation of arrows, see legend to Figure 2.

tivity per 10 presentations in the series utilizing light alone, as compared with the series utilizing the sound-light combination. Figure 7 presents these findings graphically. It will be noted that when light stimuli alone are used there is little habituation of the effects of light in suppressing alpha activity within the limits of this test period. On the other hand, when sound-light combinations are used, the effect of the light in causing obliteration of the alpha activity becomes rapidly attenuated. The plotted curves of the response of alpha activity to light under the two testing situations are significantly different (to <0.01 level). The two curves also have significant differences in shape (to <0.01 level also), showing that the responsiveness of the alpha activity to light is becoming attenuated at a significantly more rapid rate in the series of sound-light combinations than in the series in which light alone was used as a stimulus.







Figs. 4, 5, 6.—Failure of alpha activity to respond to either sound or light after repeated presentation of paired sound-light stimuli. For interpretation of arrows, see legend to Figure 2.

TABLE 1.—*Number of Times Alpha Activity Was Blocked by Light and Sound-Light Stimulation*

Presentations	1-10	11-20	21-30	31-40	41-50
Average no. of times light was followed by alpha suppression using light as only stimulus	8.5	8.1	7.6	7.6	7.6
Average no. of times light was followed by alpha suppression using sound-light combination	7.6	6.9	6.1	5.6	5.1

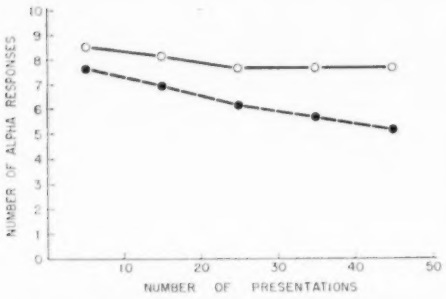


Fig. 7.—Mean number of times the presentation of light was followed by alpha suppression per 10 presentations in the series of utilizing the light stimulus alone (solid line). Mean number of times light was followed by alpha suppression per 10 presentations in the series presenting sound-light combinations (dotted line).

Table 2 presents the average duration of disappearance of alpha rhythm for each time the alpha activity was blocked by light in the two test situations. This indicates that when suppression of alpha activity did occur in either test situation, the average duration of suppression did not show a significant difference between the two groups, though the number of times the alpha activity disappeared after light differed significantly. Since some differences in the two groups are seen here, it is possible that a larger series of subjects may have led to discovery of a significant difference between these two groups.

Comment

These observations demonstrate that the suppression of the alpha activity by visual stimulation repeated a number of times is significantly reduced by the juxtaposition of a preceding auditory stimulus. The number of times that light causes disappearance of alpha activity was significantly diminished in that series in which visual stimulation was consistently preceded by a tone. In the past this has been ascribed to habituation. In view of these observations, to what extent does this hypothesis seem tenable?

The published evidence to substantiate the occurrence of habituation of the alpha response to visual stimulation in man is rather scanty. Bagchi [2] and Galambos [3] state that habituation does not occur. Gastaut and associates,[4] in their study of the topography of conditioned responses, and Roussinov and Smirnov,[5] in their review of the electroencephalography of conditioning in man, state the response of the alpha rhythm to light becomes habituated as does the response to sound, only at a slower rate. In neither study is precise evidence of this phenomenon given.

Wilson and Wilson,[6] using a single photic flash, have demonstrated that the response of the alpha activity to the single flash does not diminish significantly even when the repeated stimulus appears approximately every 10 seconds for periods as long as 30 minutes.

TABLE 2.—*Duration of Alpha Suppression Following Light and Sound-Light Stimulation*

Presentations	1-10	11-20	21-30	31-40	41-50
Average duration of suppression (sec.) of alpha using light as only stimulus	0.91	0.64	0.64	0.70	0.70
Average duration of suppression (sec.) of alpha using sound-light combinations	0.73	0.67	0.67	0.66	0.57

Though these studies utilized single flashes of light, they are similar to the studies reported here, wherein repeated stimulation by a bright light lasting three seconds shows slight, if any, habituation during 50 successive presentations at a rate of approximately once every 10 seconds. Thus, so long as the patient remains alert, there is little definite evidence at present to demonstrate that the responsiveness of alpha activity to a strong visual stimulus becomes significantly habituated.

Since the diminished effectiveness of light in suppressing alpha activity when juxtaposed with an auditory stimulus cannot be explained by the process of habituation to light alone, what, then, is the explanation for this changed responsiveness? Obviously, the closely associated sound appears to have modified in some way the usual effectiveness of the light in bringing about the disappearance of alpha activity. Three possible mechanisms are suggested, though there is no proof at present that any of these hypotheses is correct.

Pavlov [7] himself described as a manifestation of internal inhibition the situation in which the "isolated action of the conditioned stimulus, even though followed by the unconditioned, leads to the development of a state of inhibition," in which the usual response to the unconditional stimulus failed to appear. In Pavlov's animals, however, this form of internal inhibition appeared as a rule only after prolonged repetitive testing, usually for several years, during which the usual conditioned responses had been maintained. Certainly the early occurrence of these effects described here are not entirely comparable to those described by Pavlov. A second possible mechanism is suggested by the observations of Hernández-Peón, Scherrer, and Jouvet [8] on the reduction of potentials in the cochlear nucleus in response to sound when the animal was interested in some other activity. It is possible that the preceding auditory stimulus here diverts attention from the subsequent visual stimulus, but this, too, is a consideration for which there is no proof—and indeed it is rather hard to consider a situation in which attention is roused by an auditory stimulus which in itself has no effect upon the electroencephalogram. Nor does the work of Wilson and Wilson [6] support this possibility, for in their studies directing the attention of the subject to outside events had no effect upon the alpha responsiveness. Lastly, it is conceivable that the addition of a preceding stimulus to which habituation rapidly develops leads by some mechanism to a more rapid habituation of response to the second stimulus.

These observations demonstrate that a cerebral response to external stimulation which under ordinary conditions is relatively stable can be modified significantly by the juxtaposition of a preceding stimulus, the stimulus itself being insufficient to produce any noticeable change in the resting electroencephalogram. The mechanism of this changed responsiveness remains obscure, but it cannot be explained by habituation to the "unconditional" stimulus per se.

Summary

During the course of studies on the development of temporary cerebral connections in man, it was observed that with repeated pairing of sound and light stimuli, the expected suppression of alpha activity following the appearance of light often failed to occur. This has usually been ascribed to habituation. These studies were designed to determine whether habituation were a tenable explanation for these observations.

Fourteen normal subjects were at irregular intervals presented repeatedly with the same light stimulus of three seconds' duration. On another occasion, the same subjects were presented repeatedly with paired sound and light stimuli, the sound commencing one second before the appearance of the light and lasting throughout its duration.

Examination of the EEG's showed that the desynchronization of alpha activity on visual stimulation was significantly less in

the series with juxtaposition of a preceding auditory stimulus than in the series in which no sound was used. Habituation does not suffice as an explanation, since within the limits of this test series habituation to light alone was minimal. Thus this study demonstrates the ability of a preceding auditory stimulus which ordinarily has no effect upon the electroencephalogram to modify the effectiveness of a succeeding light stimulus whose usual effect is to cause suppression of alpha activity.

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Inferior Nasal Quadrantanopsia in Pseudotumor Cerebri

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Occasionally the ophthalmologist or the neurologist is confronted with a patient with bilateral papilledema associated with increased intracranial pressure for which no cause can be found, even after extensive neurologic examination and neurosurgical intervention. The signs and symptoms indicative of increased intracranial pressure simulate those of a cerebral tumor, and therefore the term "pseudotumor cerebri" has been applied to this condition. This syndrome previously has been referred to in the literature as otitic hydrocephalus, serous meningitis, intracranial hypertension, generalized cisternal archnoiditis, and toxic hydrocephalus.[1,3,10]

In many patients with pseudotumor cerebri no abnormality in visual fields is found. Of the field defects reported, the commonest is the enlargement of the blind spots.[2] Foley,[9] in his series of cases of pseudotumor cerebri, observed patients with homonomous quadrant defects, central scotomas, and constricted fields. Dunn and Baker[7] reported a case of pseudotumor cerebri that showed an inferior nasal quadrantanopsia in the right eye. Walsh[19] reported a similar case having a left inferior nasal quadrant defect.

In three cases of pseudotumor cerebri that have been observed at the Wills Eye Hospital for periods varying from 5 to 13 years, an inferior nasal quadrantanopsia was found in one eye on visual field examination. This defect occurred relatively early in two of the three cases and remained as a constant finding without progression or remission after the inciting condition had been resolved.

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Report of Cases

CASE 1.—A., a 32-year-old man, noted blurring of his vision in the left eye for three weeks prior to his admission, in January, 1946. At that time, his visual acuity was 6/6 in the right eye and 6/12 in the left eye. Bilateral papilledema, and possibly

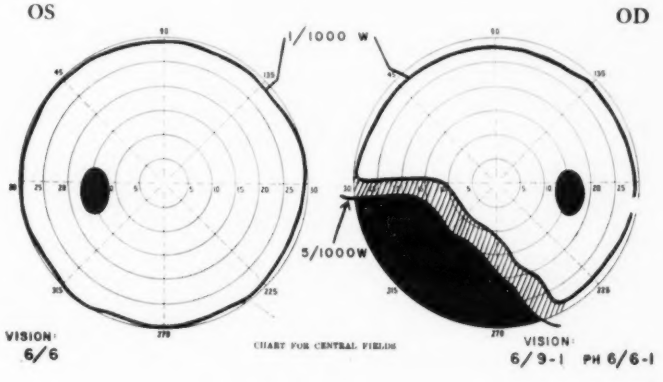

Fig. 1.—Central visual field examination in Case 1, showing marked inferior nasal quadrantic defect of the right eye.

a slight right supranuclear facial paresis, were noted. Spinal fluid examination was essentially normal, with the exception of an elevated spinal fluid pressure of 320 mm. of water. Visual field examination revealed bilateral enlargement of the blind spots and a right inferior nasal quadrant defect (Fig. 1). Ventriculography, pneumoencephalography, electroencephalography, and skull x-rays showed no abnormality.

During the next five years little change was noted in the patient's condition. In 1952 sagittal-sinus venography was performed and produced a partial left frontal lobe softening, which resembled a possible cerebral neoplasm. Left carotid arteriography also was considered to be indicative of a left frontal lobe neoplasm. On the basis of these findings, a craniotomy was performed; however, no tumor was found. After these diagnostic and therapeutic procedures, the patient developed a convulsive disorder characterized by occasional grand mal convulsive seizures, which subsequently were controlled with combined diphenylhydantoin (Dilantin) and phenobarbital medication.

In the past few years, the patient has shown slight improvement of vision. At the present time, the visual acuity in the right eye is 6/6—3 and in the left eye 6/9—4, despite definite pallor of both optic nerve heads. Visual fields have revealed persistent enlargement of both blind spots and a right inferior nasal quadrantanopsia. Spinal fluid pressure has remained elevated, with initial pressure approximating a level of 250 mm.

Case 2.—B., a 34-year-old housewife, was first seen in August, 1951, complaining of blurred vision in both eyes of one week's duration. Four months prior to this time, she had noted a similar blurring of vision, which lasted for three weeks. On examination, visual acuity in the right eye was 6/9—3 and in the left eye 6/6. Papilledema, of 3D., was noted in each eye. Visual field examination showed bilateral enlargement of the blind spots and a right inferior nasal quadrant defect (Fig. 2). Spinal fluid examination was normal except for an elevated spinal fluid pressure of 340 mm. of water. X-rays of the skull, ventriculography, and pneumoencephalography were all within normal limits.

Since the condition of the patient showed little improvement by January, 1952, roentgenography of the superior sagittal and transverse sinuses was performed; however, no abnormality was found. A right internal carotid arteriogram was then obtained, but this, too, was normal. In view of the right inferior nasal quadrant defect, as well as the persistent elevation in the cerebrospinal fluid pressure and the advancing papilledema, a right frontal craniotomy was performed in April, 1952. No tumor was found. Following this surgical procedure, however, the patient experienced complete relief of the pressure sensation in her head. The papilledema subsided, leaving a residual pallor of the right optic nerve head. The patient has since been seen at frequent intervals and has shown continued improvement. Visual acuity presently is 6/9—1 in her right eye and 6/6 in her left eye. The right inferior nasal quadrant defect has remained unchanged on reexaminations of the visual fields.

Case 3.—C., a 25-year-old woman, was first seen in March, 1954, with the chief complaint of redness, pain, and photophobia in her left eye and bilateral frontotemporal headaches for several weeks. Examination revealed a diminished right patellar reflex, slight weakness of the right leg, and bilateral papilledema. Visual acuity in each eye was 6/6. Visual field examination revealed bilateral enlargement of the blind spots. Spinal fluid examination was within normal limits except for an elevation of the spinal fluid pressure to 240 mm. of water. Skull x-rays, ventriculography, and pneumoencephalography revealed no abnormality. Electroencephalography showed generalized slowing of a nonspecific nature.

A diagnosis of pseudotumor cerebri was made at that time. The patient was seen at frequent

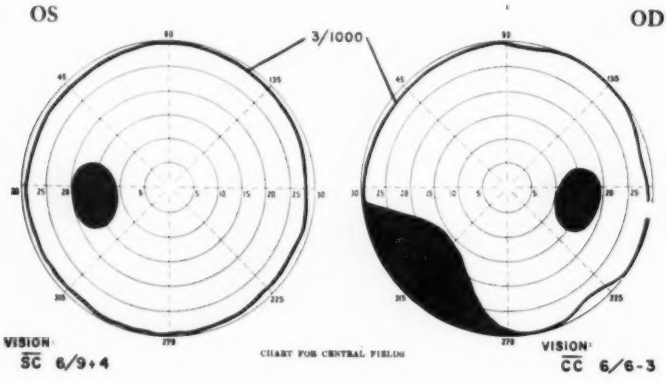

Fig. 2.—Central visual field examination in Case 2, showing moderate inferior nasal quadrantic defect of the right eye.

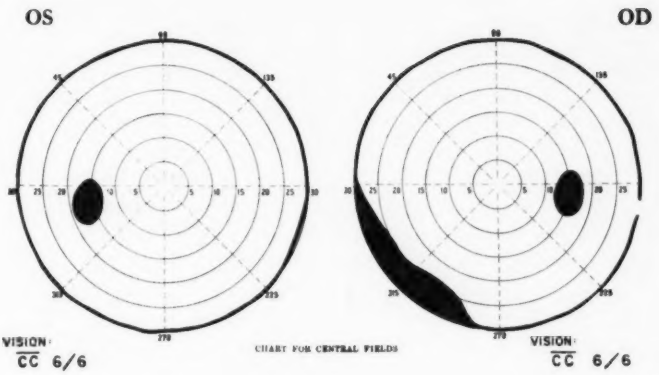

Fig. 3.—Central visual field examination in Case 3, showing slight inferior nasal quadrantic defect of the right eye.

intervals during the next four months, and her condition showed improvement. She continued, however, to experience severe recurrent headaches approximately every three or four months, which were relieved by repeated lumbar punctures. The spinal fluid pressure at the time of these examinations varied between 200 and 260 mm. of water.

Her response to this conservative treatment has been excellent, and the previously existing papilledema has completely subsided. Early in 1957, a repeat visual field examination revealed for the first time a slight but definite right inferior nasal quadrant defect (Fig. 3), which has been found on subsequent examinations. Presently, her visual acuity in each eye is 6/6. During the past year, the headaches have subsided, and the spinal fluid pressure has been within normal limits.

Comment

Many explanations have been proposed concerning the etiology of pseudotumor cerebri. Symonds [16] postulated that this condition resulted as a complication of otitis media. Some authors have suggested thrombosis of the superior longitudinal sinus or the major lateral sinus as the precipitating factor.[9,14,15,18] Dandy [2] believed that the condition was produced by transient vasomotor changes with cerebral edema. Wagener,[18] McCullagh,[13] and Davidoff [3,4] reported several cases of pseudotumor cerebri associated with menstrual edema. Foley [9] described this syndrome occurring during pregnancy, as well as prior to and after miscarriage. Devanney and Shea [5] reported a case believed to be due to allergic encephalopathy. Despite these many hypotheses, the etiology of pseudotumor cerebri in the majority of cases remains obscure.

The findings simulate those of an intracranial expanding lesion, with the characteristic signs and symptoms of increased intracranial pressure. Headaches, failing vision, diplopia, unilateral or bilateral abducens palsies, dizziness, nausea, vomiting, and bilateral papilledema are some of the commoner signs and symptoms of this disorder.[1,3,8,9]

Cerebrospinal fluid examination is completely within normal limits except for an elevation in the spinal fluid pressure. X-rays of the skull and pneumoencephalograms show no abnormality. Ventriculography reveals a normal or smaller-than-normal ventricular system with no displacement.[7] Electroencephalography may be normal or may reveal an abnormal record of a nonspecific nature.[14] In some cases superior sagittal venograms may show an obstruction in the posterior part of the sagittal sinus.[1]

In the majority of cases the prognosis is excellent, and the recovery may be spontaneous, with no further symptoms. However, if visual loss is threatened, owing to advancing papilledema, and if severe intractable headaches persist, lumbar punctures repeated at varying intervals may be effective in the treatment of this disorder. Other authors believe that a subtemporal decompression should be performed.[8,19] Dehydration measures, namely, restriction of

the salt and fluid intake and the administration of acetazolamide (Diamox) or ammonium chloride have also been suggested.[4,7] In cases of thrombosis of the dural sinus, surgical removal of the thrombus is indicated, followed by the use of anticoagulant therapy.[14,15]

It is generally agreed that the visual field defects in pseudotumor cerebri are a direct expression of the pathologic changes in the optic nerve and optic nerve head. Traquair [17] has suggested that the peripheral contraction of the visual field is due to interstitial changes in the optic nerve and is, as a rule, severer peripherally, with a tendency to spread inward, resulting in a diminution of the blood supply to the nerve fibers in that area.

Another possible explanation for this inferior nasal quadrant defect may be on a mechanical basis, wherein the optic nerve is displaced against the edge of the optic canal, owing to the existing edema, with resulting compression of the superior temporal portion of the nerve.[7]

A more plausible explanation has recently been offered by Hughes,[11] who believes that these field changes are on the basis of gliosis of the nerve head, resulting in secondary optic atrophy following papilledema. Presumably, this process commences in the glial sheath of the nerve head on the temporal side, often as a wedge of fibrous tissue, and gradually spreads around the nerve like a collar. The periphery of the lower nasal field is first affected, and the involvement, if continued, can spread upward, resulting in a severe nasal hemianopia.

Both Hughes [11] and Duke-Elder [6] are of the opinion that once gliosis of the nerve head occurs, it tends to be progressive, eventually producing concentric contraction, chiefly on the nasal side of the field. This was not found to be true in the three cases presented in this paper. The inferior nasal quadrant defect has remained essentially unchanged on repeated examinations up to the present time. This observation was also noted by Walsh in a case of pseudotumor cerebri in which the inferior nasal quadrantanopsia remained as a constant finding for over 24 years.[19]

It is true that the commonest field change in papilledema is enlargement of the blind spots; however, unless the periphery of the nasal field is carefully tested, the depression in this area will often be missed.

Summary and Conclusions

In some patients who otherwise manifest the usual clinical features of pseudotumor cerebri, there is observed a visual field defect in the form of a unilateral inferior nasal quadrantanopsia. Three such cases are described that have been observed at the Wills Eye Hospital for periods varying from 5 to 13 years. It has been found in these instances that the inferior nasal quadrant defect remains essentially unchanged, without progression, and that it is not a threat to vision provided the original condition has been completely resolved. Emphasis is placed upon the need to recognize the inferior nasal quadrantanopsia as a sector type of visual field defect which, in the presence of increased intracranial pressure, has no localizing significance and does not warrant exploratory neurosurgical intervention.

Of several possible explanations considered, the one preferred is the concept of a gliosis of the optic nerve commencing in the glial sheath of the nerve head on the temporal side.

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Obituaries

HARRY LEE PARKER, M.D.

1894-1959

Harry Lee Parker, consulting neurologist at the Mayo Clinic from 1925 to 1934, and from 1945 until his death, in 1959, was born on Feb. 20, 1894, in Limerick, Ireland. When the boy was 7 years old, he moved with his parents to Johannesburg, South Africa, where he completed his preparatory work for college. In 1916 he received the degree of bachelor of arts and in 1918 the degrees of bachelor of medicine, bachelor of surgery, and bachelor in the art of obstetrics from Trinity College, Dublin, and the licentiate in medicine from Rotunda Lying-in Hospital. In 1918 and 1919 he served in France in the Royal Medical Corps of the British Army.

Dr. Parker came to Rochester, Minn., in November, 1919, as a fellow in surgery in the Mayo Foundation. He transferred his major interest to neurology in July, 1921. He received the degree of master of science in neurology from the University of Minnesota in 1923, and in January, 1924, he was appointed to the staff of the Mayo Clinic as a consultant in neurology. He was an associate professor of neurology in the Mayo Foundation, Graduate School, University of Minnesota, when he left the Mayo Clinic in 1934.

In 1934 he returned to Dublin to become honorary professor of neurology at Trinity College, staff physician at the Richmond, Whitworth and Hardwick Hospitals, Stewart Institute for Feebleminded Children, Bloomfield Mental Hospital, and Royal Hospital for Incurables, and he was consulting neurologist at the Meath, Mercer's, and Orthopaedic Hospitals. He received the degree of doctor of medicine from Trinity College in 1945.

Dr. Parker was a charter member of the Central Neuropsychiatric Association, a fellow of the Royal College of Physicians of Ireland and of the Royal Society of Medicine of England, and a member of the American Neurological Association, the Association of British Neurologists, and the Royal Academy of Medicine in Ireland. At different times he was a member of the American Medical Association and the British Medical Association. In August, 1945, he returned to the Mayo Clinic, from which he would have retired on March 31, 1959.

Dr. Parker had a sensitive, warm, and friendly nature; he was endowed with intelligence of a high order, and he had both imagination and facility in speaking and writing. He was fond of declaiming passages from Shakespeare, Marlowe, and John Donne, and he knew most of the leading figures in the Irish literary world. He made many contributions to the literature on neurology, but his literary skill is nowhere more evident than in his volume "Clinical Studies in Neurology," published in 1956. This book was based on a series of lectures which he gave to medical students in Dublin. It is informal and witty, and contains many historical allusions and vivid local color, but, at the same time, is a forthright scientific work of value to the student and a source of much enjoyment to the seasoned neurologist.

In his later years Dr. Parker suffered from emphysema, which led to increasingly frequent periods of disability. He died in Rochester on March 1, 1959. He was widely known as an outstanding clinician and teacher, and his intimates knew him as a warm friend and brilliant conversationalist who viewed his own physical infirmities with admirable equanimity.

JOHN B. DOYLE, M.D.

Books

A Manual of Electrotherapy. By Arthur L. Watkins, M.D. Price, $5. Pp. 259, with 167 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia, 1958.

This book is basically a revision and condensation of Dr. Richard Kovacs' large textbook "Electrotherapy and Light Therapy," with the addition of a section describing the use of ultrasonics in physical medicine. Many of the outdated sections have either been completely omitted or radically revised. In some instances, the original was not sufficiently modified to comply with present clinical practices. For example, the large electric heat cabinet for general body radiation is rarely, if ever, medically indicated according to current trends, although, obviously, certain patients feel more relaxed following such a session; the same effect can usually be accomplished more efficiently by other physical or pharmacologic means.

The title, "A Manual of Electro*therapy*," is somewhat misleading, since there is a chapter on electrodiagnosis which would be of more interest to the neurologist than the other sections of the book. Even this chapter, however, emphasizes the older techniques, some of which are of little practical value. The more useful strength-duration and chronaxie measurements are described under the section "Newer Methods of Electrodiagnosis." These techniques are not new but are important basic procedures which are frequently helpful in the complete analysis of a problem involving the lower motor neuron. Such a section could better be reserved for further description of electromyography, and for a mention of the newer techniques and possible indications for measurement of nerve-conduction velocity, bearing in mind that such procedures are helpful only when properly correlated with a thorough clinical evaluation.

Despite the above minor shortcomings, the book is lucidly written, so that it can serve as more than a "*Manual* of Electro*therapy*" for all professional persons interested or involved in the care of patients requiring the use of electrical modalities.

KENNETH C. ARCHIBALD, M.D.

Therapeutic Electricity and Ultraviolet Radiation. Edited by Sidney Licht, M.D. Volume IV of the Physical Medicine Library. Price $10. Pp. 343, with 94 illustrations. E. Licht, 360 Fountain St., New Haven, Conn., 1959.

This book, which is Volume IV of the "Physical Medicine Library" series, is undoubtedly the most recent comprehensive textbook on therapeutic electricity and ultraviolet radiation. This volume does not include electrodiagnostic procedures, the subject of Volume I of the series, or "Therapeutic Heat," the title of Volume II. It deals basically with electric stimulation and ultraviolet radiation. The neurologist would be most interested in the excellent chapter on clinical electric stimulation by Dr. G. Keith Stillwell. In this chapter the nature of electric stimulation is discussed, along with the rationale for its use primarily in denervated skeletal muscle but also in other clinical situations. Animal studies aimed at determining the minimal amount of electric stimulation that can provide the optimal retardation of atrophy are described, along with the reasons for teaching certain patients how to use a simple home stimulator.

For those intrigued by the physics of instrumentation, the chapter on this subject by Stuart Reiner, an extremely clever electrical engineer, is well written but probably too technical for the clinician without this unusual interest. He makes a special attempt, however, to keep explanations and circuit diagrams basic and clear.

As in the previous volumes of this series, Dr. Licht's keen interest in medical history is evidenced by his thorough review of the history of electrotherapy and ultraviolet radiation. Through his efforts, the Yale Medical Library undoubtedly has the largest collection of old books on these subjects ever to be found. Perusal of this collection is not only enlightening but also entertaining. I am sure many of the 923 listed reference books on the subject of electrotherapy would elicit a feeling of combined sympathy for both patient and physician when considered in the light of more recent advances and trends.

The technique and use of "electrosleep therapy" in psychiatry is described in a short chapter, following a good discussion of iontophoresis.

The section on ultraviolet radiation would be of greater interest to the dermatologist than to the neurologist, although both would be interested in the description of its use for herpes zoster and decubitus ulcers.

In summary, this volume of the "Physical Medicine Library" series serves as a good basic reference text in physical medicine along with the other three volumes (Volume I: Electrodiagnosis and Electromyography; Volume II: Therapeutic Heat; Volume III: Therapeutic Exercises). Although this particular volume contains a smaller amount of practical information than the others, the entire four-volume series should be readily available in the library of any professional unit or person who may become involved in the diagnosis or management of patients with neuromuscular or musculoskeletal problems.

KENNETH C. ARCHIBALD, M.D.

Biological and Biochemical Basis of Behavior. Edited by Harry F. Harlow and Clinton N. Woolsey. Price, $8. Pp. 476. The University of Wisconsin Press, 811 State St., Madison, Wis., 1958.

This volume contains the papers presented at a symposium on Interdisciplinary Research as it applies to behavior, held at the University of Wisconsin. It was published on Dec. 5, 1958. The preface opens with a provocative sentence, "One of the most important developments in the biological sciences during the last fifty years has been the growth of interdisciplinary research." Cited are the illumination that has resulted from the correlation of psychological and anatomic data, and, as more recent evidence of triumph, the fruits of correlation of behavior with data from other biological sciences. The volume is beautifully put together, well printed and arranged, and contains the facts and views of a number of able investigators.

Its faults are those of many printed proceedings of symposia—the articles could be shortened and the facts more incisively and clearly presented. In part for the reason of wasted pages, the remarks of the discussants, a most important aspect of a symposium, had to be omitted. Third, because of obvious difficulties with editing and final changes, the proceedings become available to the reader much too late. One of the most important reasons for publishing a symposium is thus lost, since it is the freshness, intimacy, and the shaping and exchange aspects of the meeting that give the printed pages their value.

This reviewer always has difficulties with the phrase "interdisciplinary research." There is no controversy if by this is meant that the most exciting research is often done on the border between disciplines by a man who has encompassed two disciplines, though primarily knowledgeable in one. Or, if it means that an investigator creative in one discipline has found, through limitations and frustration, an awareness of the potential usefulness to him of the methods of another discipline and can then interest as a co-worker the enthusiasm of a person in this other discipline, much can be expected. The questions asked and the formulation are still mainly the outcome of the efforts of one of the group. But if it means a "team" of experts, each a member of a project, confronted by the general area of investigation and each employing his method to explore what he can, with the hope that the pooled results will be remarkable, then little comes of the combined effort, even though some parts may be independently valuable. To be sure, "development" of an original observation, such as the large-scale production of an important antibiotic or the production of a hormone synthesized by one man, is very much enhanced by a team of specialists, each contributing what he knows to the specific problem of increasing or purifying the yield. But this is not the explorative research now so basic to the furthering of behavior as related to other biologic phenomena.

However, late or otherwise, this volume is a valuable one. The contributors are scholarly, and their work indicates new directions of thought in physiology, psychology, and biochemistry. For example, one of the interesting contributions is that of Rosenzweig, Krech, and Bennett on some biochemical accompaniments, within the cerebral hemispheres of behavior phenomena. It was shown by these authors that the cholinesterase content of brain, a biologic indicator of uncertain significance, is distributed unevenly in the projection areas of the cortex of rats. Compared were samples of lesions from the visual, motor, and sensory cortex in young and old rats. Also samples from rats with different preferred methods of solving maze problems were compared with each other as regards the relative amount of the cholinesterase in these separate portions of their cortex. The authors report finding that age and site made for differences in cholinesterase content, but, most interesting,

that rats with a preference for one method of solving a problem had a different enzyme content in the same area than did rats with another preference. It is not surprising that cytologically different cells should contain different amounts of enzyme (note that the areas studied were projection areas and no inferences may be drawn about differences in the chemical structure of cells in different portions of the isocortex of these or other animals). But it is stimulating to know that differences in degree of functional activity in a specific aggregate of neurons can now be chemically, as well as electrically, examined.

The best papers in the volume illustrate the value of borderline research done by one thoughtful man knowledgeable in two fields or by two persons working together. There are several papers on the nature of research as it applies to behavior that are entertaining and well written. This volume should be read by those interested in behavior, and especially by those who think about behavior in terms of future research.

HAROLD G. WOLFF, M.D.

Pediatric Neurology. By Stanley S. Lamm, M.D., Clinical Professor of Pediatrics, State University of New York College of Medicine at New York City, Brooklyn; Neurological Consultant, Pediatric Department, Kings County Hospital (State University Division), Brooklyn; formerly Instructor in Neurology, Long Island College of Medicine, Brooklyn; Director, Cerebral Palsy Clinic, Long Island College Hospital, Brooklyn. Price, $12.90. Pp. 495, with 22 illustrations. Landsberger Medical Books, Inc., 51 E. 42d St., New York, 1958.

The size of a textbook is important. A number of medical ones are too large and heavy for easy handling and transportation and so may be left on the shelf. Not so for this one, which measures 9¼×6¼×1 in. There are two reasons for this size. First, the subjects of anatomy and methods of examination of the nervous system, so adequately presented in other books, are omitted. Second, words are conserved by skillful usage and confinement of clinical descriptions to what is typical, while leaving subsidiary details to be found in a large and up-to-date list of references. There is no sacrifice of comprehensiveness to smallness in this book.

A textbook may be defined as a presentation of all the concepts that can be derived from the assemblage and classification of all of the facts within the scope of the subject. Any reader with experience in pediatric neurology would conclude without hesitation that the author has accomplished this purpose. He would add, too, that he has done so in a manner that makes for ease of reading and memory retention, through conciseness, definitiveness, and coherence. The chapters on Mental Growth and Development, Mental Retardation, Developmental Defects, and Cerebral Palsy, which, after all, constitute the backbone of this overlap of pediatrics and neurology, are particularly outstanding and full of new concepts.

The first edition of a textbook is never without faults, and a reviewer should be duty-bound to point them out. Here they are. There is strong objection to the insertion of Migraine in the chapter entitled Convulsive Disorders. Migraine is not a convulsive disorder. Although there is controversy about its etiology, the establishment that its mechanism is vascular gives a solid reason for placing it in the chapter on Vascular Disorders. Of the 22 illustrations, all photographs, 5 are useless because of lack of detail (Figs. 2, 4, 6, 15, and 21). Figure 19, that of a girl with pseudohypertrophy of the calf muscles, would have better illustrated the muscular disproportion had her dress been removed.

The ramifications of pediatric neurology being wide, it is predicted that this book will be used extensively by medical students, pediatricians, neurologists, psychiatrists, orthopedists, psychologists, and sociologists.

HENRY S. DUNNING, M.D.

Advances in Veterinary Science. Volume III. Edited by C. A. Brandly and E. L. Jungleer. Price, $13.00. Pp. 579. Academic Press, Inc., 111 Fifth Ave., New York 3, 1957.

Attention is called to the second article, in Volume III of "Advances in Veterinary Science," entitled "Diseases of the Central Nervous System of Domesticated Animals and Comparisons with Human Neuropathology," by J. R. M. Innes and L. Z. Saunders. The authors have attempted to classify the neuropathological disorders of veterinary science. They admit that their catalogue is incomplete, although it is indeed very extensive. Their task is complicated by the paucity of exhaustive pathological study of neurological diseases

of animals. They point out that economic factors have dictated an emphasis on infectious diseases.

As a review of diseases of the nervous system of animals, the article has much to recommend it. It contains many references to comparative neuroanatomy and extensive reports of unpublished, as well as published, cases of animal nervous system disease. It is well illustrated and has a bibliography of over 600 articles. Critical reviews of many case reports and research studies are done with care, but their number and detail detract from the attractiveness of the paper for one with a less specialized interest. On the other hand, these enhance its value as a reference for comparison of human with animal diseases of the nervous system and neuropathology. The authors point out, first, the difficulty of neurological evaluation of animals, with consequent difficulty in correlation with postmortem findings, and, second, the necessity for careful, comprehensive pathological study of interesting cases as an essential step in the understanding of the disease process. The existing lack of detailed observations and the inadequacy of most pathological studies in animals are deplored. However, a number of analogous diseases in different species, including the human, and the benefit to be gained for human neurology from veterinary work are pointed out. Animal diseases are a fertile field for study of certain basic tissue reactions, and for illumination of why and where disease in various species differs.

This thought-provoking essay will have more interest and value for the neuropathologist than for the clinician.

RICHARD DOYLE

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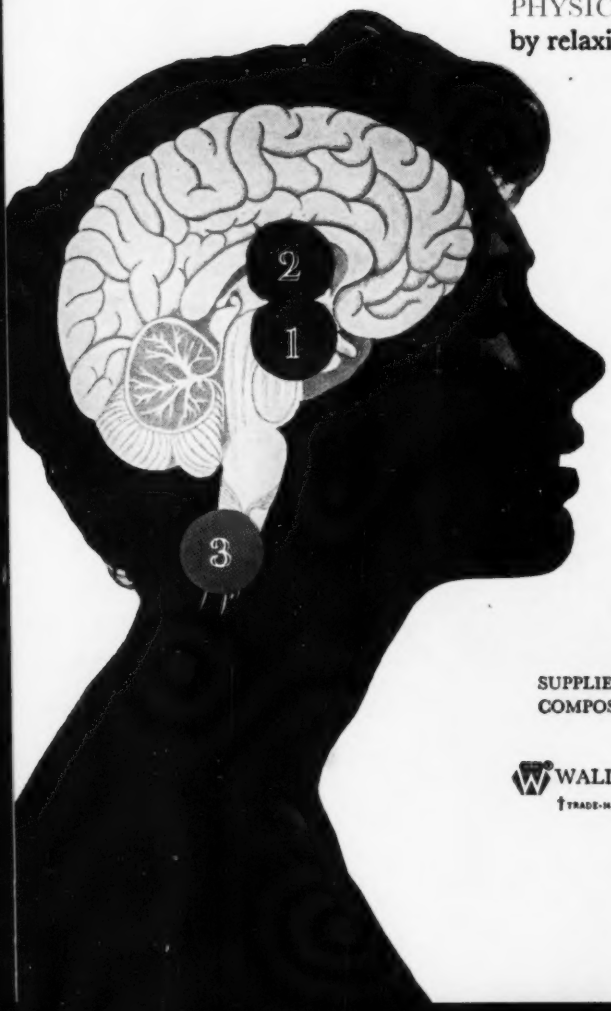

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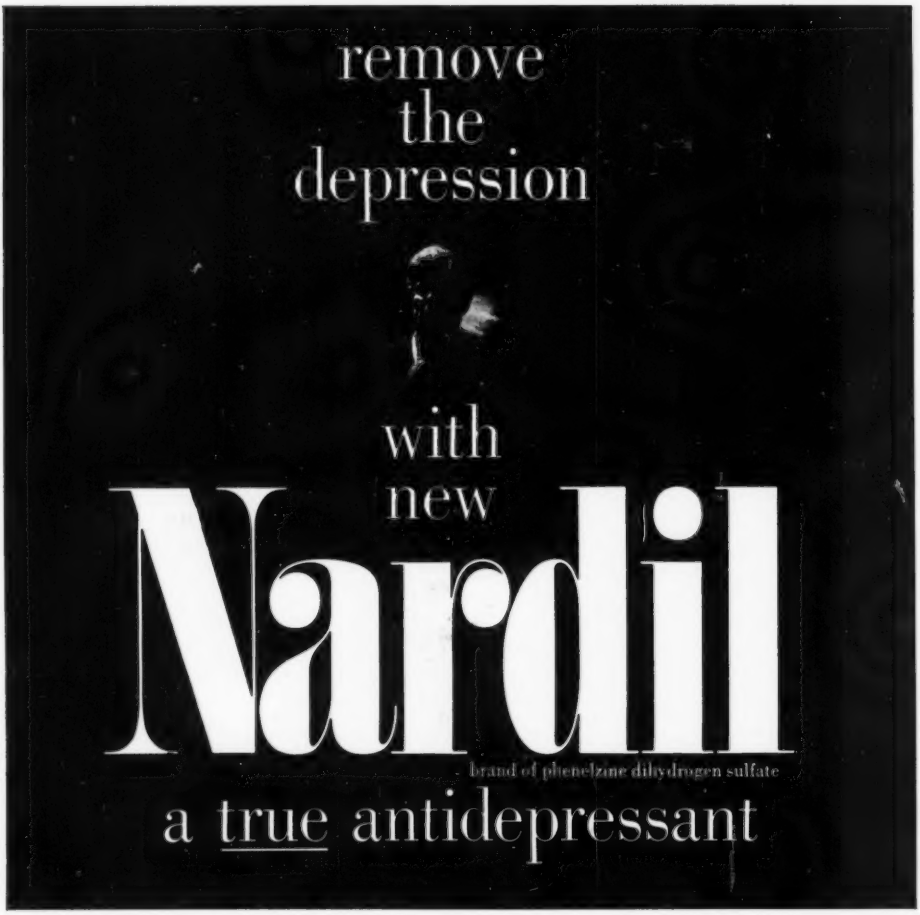
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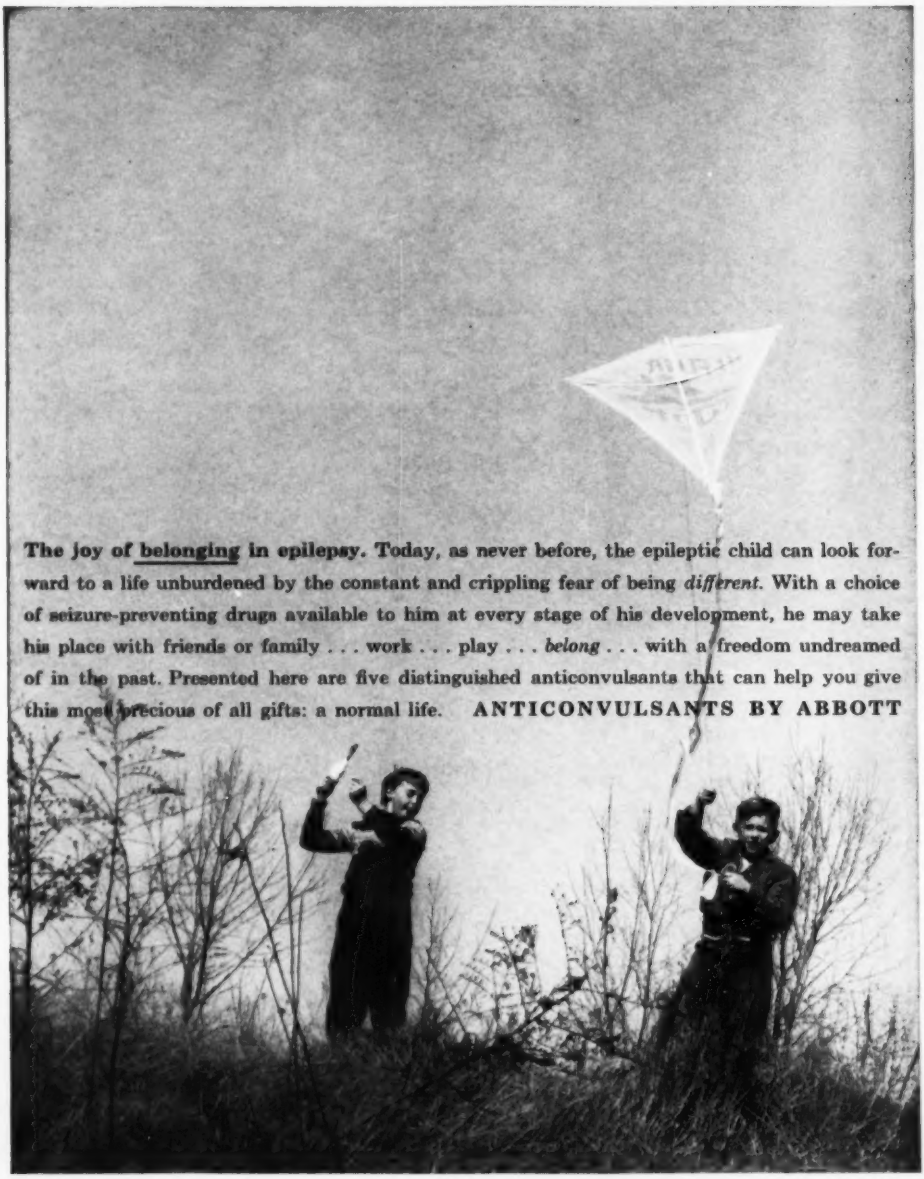
references: 1. Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. 2. Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System* 20:197 (May) 1959. 3. Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* 116:71 (July) 1959. 4. Arnow, L. E.: Phenelzine: A Therapeutic Agent for Mental Depression, *Clinical Med.*, 6:1573 (Sept.) 1959. 5. Dickel, H. A.; Dixon, H. H.; Shanklin, J. G., and Dixon, H. H., Jr.: Tension Fatigue States and Their Adjunctive Treatment Using Nardil, *Clinical Med.*, 6:1579 (Sept.) 1959.



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Rudy, L.H.; Rinaldi, F.; Costa, E.; Himwich, H.E.; Tuteur, W., and Glotzer, J.: Trifluoperazine in the Treatment of Psychotic Patients, Am. J. Psychiat. *115*:364 (Oct.) 1958.

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Madgwick, J.R.A.; McNeill, D.L.M.; Driver, M., and Preston, G.C.: 'Stelazine' (Trifluoperazine), A Preliminary Report on a Clinical Trial, J. Ment. Sc. *104*:1195 (Dec.) 1958.

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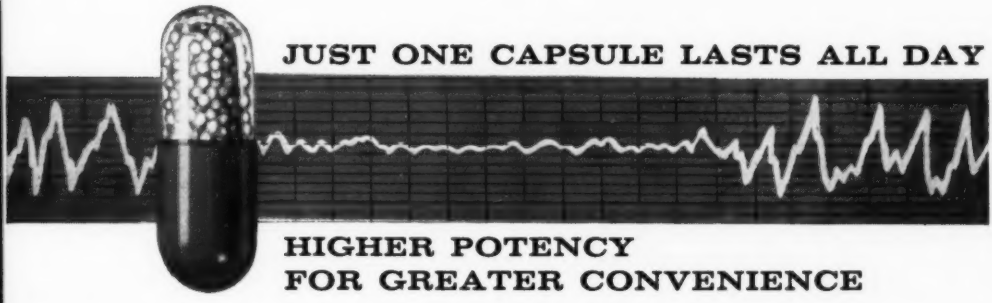

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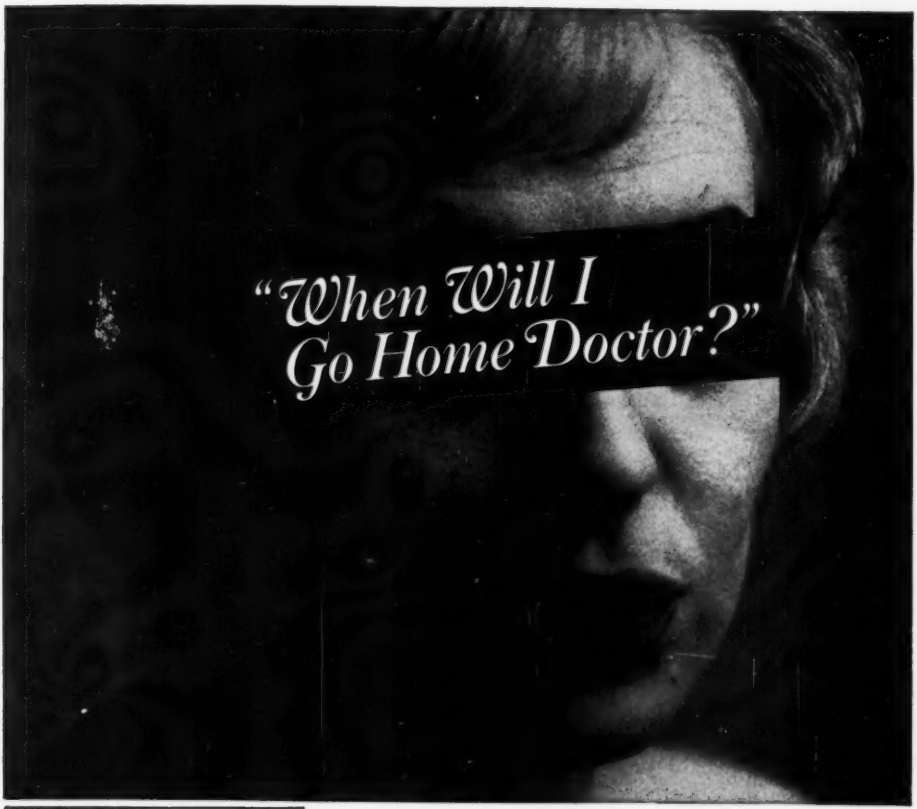

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1. Goldman, D.: Am. J. M. Sc. 235:67 (Jan.) 1958. 2. Morehouse, W. G. and Freed, J. E.: Monographs on Therapy 3:32 (May) 1958. 3. Leger, Y.: Union Med. Canada 87:831 (July) 1958. 4. Bruckman, N. S.; Saunders, J. C., and Kline, N. S.: Monographs on Therapy 3:24 (May) 1958.

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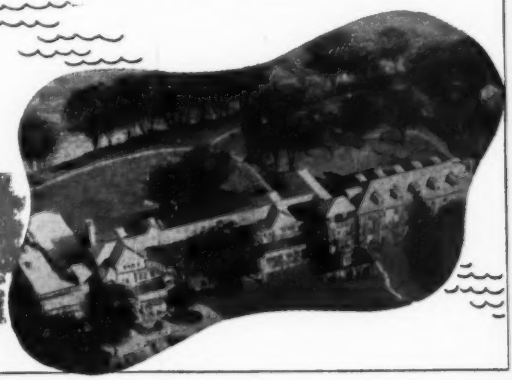

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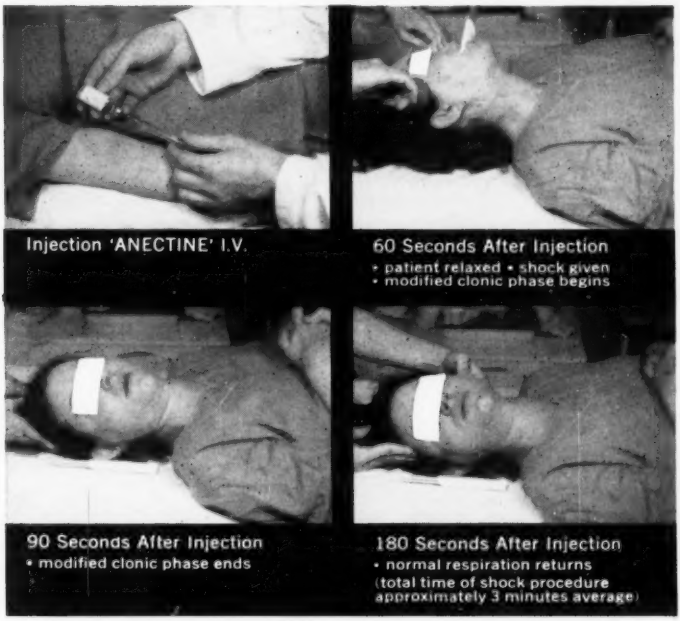
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Comments from the literature:

"**. . . method of choice.**"

Havens, L. L.: Dis. Nerv. System *19*:1 (Jan.) 1958.

"**. . . recommend its use.**"

Impastato, D. J., and Gabriel, A. R.: Am. J. Psychiat. *114*:698 (Feb.) 1958.

"**. . . treatment of choice.**"

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"**. . . irrespective of age.**"

Robie, T. R.: J. M. Soc. New Jersey *52*:82 (Feb.) 1955.

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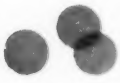

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